Vol. 36 No. 187 June, 1961

ARCHIVES OF DISEASE IN CHILDHOOD

EDITORS
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LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

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A LONGITUDINAL STUDY OF THE GROWTH AND DEVELOPMENT OF PREMATURELY AND MATURELY BORN CHILDREN

PART VII: MENTAL DEVELOPMENT 2-5 YEARS

BY

CECIL MARY DRILLIEN

From the Department of Child Life and Health, University of Edinburgh

(RECEIVED FOR PUBLICATION AUGUST 17, 1960)

This paper describes the mental development between the ages of 2 and 4 years of singletons and twins of different birth weight. The children, who were born in the years 1953 to 1955, are included in a longitudinal study of growth and development, now in its seventh year. Details of selection and procedure are given elsewhere (Drillien, 1958). Of the 600 children originally enrolled, 92% of surviving children remained in the survey at 3 years, and 90% at 4 years. The children have been examined at home at six-monthly intervals up to the age of 2, and yearly thereafter. Children who appeared to be retarded at 2 years, or who have a physical defect affecting development, have been seen every six months up to 4 years. Others who were uncooperative in mental testing at 3 or 4 years were re-examined six months later.

Method

Mental Testing Employed. A selection of tests based on the Gesell scale (Gesell and Amatruda, 1941; Gesell, 1940) with some items from the Terman-Merrill L form scale (Terman and Merrill, 1937) have been used. In addition, a full developmental history has been taken from the mother at each visit.

In selecting or rejecting certain standard test items, it was necessary not only to consider which tests were acceptable to the child and easily applied in the home, but also which tests were acceptable to the mother. The continued co-operation of the mother was thought to be of more importance than the application of a full standard scale, in cases where she appeared to resent a too obvious probing into her child's ability. For this reason it was considered diplomatic to avoid tests where absolute failure was evident to the mother (e.g. digit and sentence repetition, picture and object memory) and utilize those tests where some degree of success was to be expected, and where a qualitative as well as a quantitative assessment could be made. The developmental age was assessed not only on test response, but also on the mother's history, and on observation of the child's behaviour and speech throughout the interview. In assessing verbal responses and the history of speech and social development allowance was made for the type of home, amount of opportunity, and the type of speech which the child heard at home.

For statistical purposes the estimated D.Q. (Developmental Quotient) has been recorded as an exact number, but it is considered that pre-school testing can do no more than allot the child to certain broad groups, with some inevitable overlapping between groups, as follows:

(1) D.Q. <60 = gross defect.
(2) 60-69 = mental retardation: ineducable in normal school.
(3) 70-79 = border-line defect.
(4) 80-89 = dull.
(5) 90-99 = low average.
(6) 100-109 = average or good average.
(7) 110 and over = superior.

A brief description of points elicited in taking the history and tests used at 3 and 4 years is given below, with responses expected for the child of average ability. Retarded children were tested at a lower level, as described in a previous paper (Drillien, 1959). It was not possible to test children of superior intelligence through the full range of their ability, except in a few cases where the mother was sufficiently interested to allow the test to be done alone with the child.

History*

(1) Locomotion. At 3 years the child is reported to run well without stumbling, pedal and steer a tricycle, jump on both feet off a low step, and walk up and down stairs independently. He usually walks up alternating feet to consecutive treads, and down bringing both feet to the same tread and holding on to the wall or rail. At 4 years he runs up and down stairs alternating feet, and will jump the last two or three steps.

* As expected for a child of average ability.

(2) Speech. At 3 years he is reported as speaking in short complete sentences, with only minor defects of construction (e.g. 'me' for 'I'). Pronunciation may not be perfect, but the child is comprehensible to strangers. With some prompting at beginnings of lines he can repeat a few rhymes, songs or commercials from the television. By 4 years he is able to use quite long, well constructed sentences, and repeats rhymes with little help.

(3) Social

Feeding. At 3 years the child feeds himself with little spilling, using a spoon and fork. He holds his cup by the handle, and pours from a jug. At 4 years, if allowed, he can use a knife.

Dressing. At 3 years he pulls off shoes, socks, and pants, undoes accessible buttons, and can put on shoes (not always on the correct feet). At 4 years he can dress and undress with little assistance, can fasten buttons and buckle his shoes.

Toilet. By 3 years he is reliable by day, and will go to the toilet alone, but still needs help with wiping, and adjusting clothes. He is usually dry at night without lifting by 3½ years, and at 4 years will take full responsibility for his toilet needs.

Testing Procedure

(1) Speech

(*a*) 18 coloured pictures of common objects: at 3 years he names 12+, and at 4 years 16+.

(*b*) Six action pictures (e.g. a boy throwing a ball, a girl pouring tea): in answer to the question 'what is the boy doing?' the 3-year-old will give some indication of action in three or more pictures (e.g. 'playing', 'getting tea') and names objects freely. At 4 years actions are described for five or six at a more advanced level (e.g. 'he's throwing the ball up in the sky', 'she's pouring tea for her dollies').

(*c*) Comprehension questions: uses of five common objects (penny, matches, spoon, ball, pencil). In answer to the question 'what do we use this for?' the 3-year-old responds to 3+ at a simple level (e.g. 'sweeties', 'smoke it') and the 4-year-old to all five, at a more advanced level (e.g. 'to buy a lollipop', 'light the gas'). In answer to the questions 'what must you do when you are hungry? tired? cold?' the average 4-year-old will respond correctly to at least two, and to the questions 'why do we have books? houses?' to at least one.

(2) Adaptive

(*a*) Block building: he will build a tower of nine to 10 at 3 years. A bridge is imitated at 3+ years, and copied from a model at 4 years. Blocks are also used for colour and counting.

(*b*) Drawing: most 3-year-olds will hold the pencil correctly. At this age they can copy a circle and imitate a cross. At 4 the child will copy a cross, may attempt a square, and score 1+ on the incomplete man test.

(*c*) Colour forms: a score of 3+ is expected at 3 years; a demonstration of the circle may be needed.

(*d*) Geometric forms: the 4-year-old scores 8+.

Correlation between Pre-school Testing and Intelligence Testing in School

A full analysis of the predictive value of early developmental testing in children of different birth weight from different types of home will be carried out when the necessary data have been obtained for the whole group. It is also hoped to relate school performance to observed pre-school and early school ability in children from different types of environment. However, it was thought useful to examine briefly here the findings in those children born in 1953 and 1954 who have already been tested in school.

To date 206 children who were adequately tested at 3 and/or 4 years have been given the Terman-Merrill L form test. The biggest disparity in scores was found in 18 cases who were considered superior (i.e. D.Q. 110 to 120) at 3 to 4 years, and scored 125 to 140 on the T.M.L. test. After excluding these cases, 68% of the remainder showed a disparity of eight points or less between the average of the 3 and 4 year tests and the T.M.L. test (Table 1). In all, 60 children showed a disparity of more than eight points. Of these, 33 stayed in the same broad grouping or moved up or down one group, there being no change in expected school disposal. In these cases the difference in scores was between nine and 14 points. Twenty-seven children (13%) showed a disparity of 15 points or more. Seven children scored higher in the pre-school period; of these, six are under supervision at a child guidance clinic for behaviour problems in school, and the seventh suffered a major domestic upheaval shortly before school entrance. It seems likely that the T.M.L. score is an underestimate in these cases. Twenty children scored 15 points or more lower at 3 to 4 years. Of these, five had suffered marked deprivation in the pre-school period (e.g. death or desertion of the mother, gross neglect, or attendance in a day or residential nursery since birth). Five showed slow development in speech, and were saying practically nothing at 3 years, although average in other respects, or had speech defects rendering them incomprehensible at 4 years. One

TABLE 1

DIFFERENCE BETWEEN AVERAGE OF D.Q. SCORES AT 3 AND 4 YEARS AND T.M.L. SCORE AT 5 PLUS YEARS

Points Difference	No. of Cases	%	Cumulative %
0– 4	78	41	41
5– 8	50	27	68
9–12	22	12	80
13–16	20	11	90
17–20	11	6	96
21 and over	7	4	100

small premature from a good home showed steady improvement from 6 months. Her scores at 1, 2, 4, and 5½ years were 61, 94, 100, and 120 respectively. Seven children (3·4%) who were tested adequately at 3 and 4 years, and appeared to be definitely slow, in the absence of unfavourable environmental influences which might affect development, were considered to be average or good average in school.

Correlation coefficients between pre-school tests at different ages and T.M.L. testing in school are given in Table 2. Considering that more than half of the children tested were premature infants, many of whom tended to improve between 6 months and 4 years, and also the inability to carry out full testing on children of superior ability, the correlations obtained are remarkably high. The correlation for test–retest on the Terman-Merrill L against M form at the same age is given as 0·88 in the age period 2 to 6 years (Terman and Merrill, 1937).

The agreement at the lower end of the scale is very close, as shown in Fig. 1. Sixteen children are considered to be ineducable in normal school (T.M.L. <70); of these, 12 were assessed at this level at 6 months and at every examination thereafter; no child scored higher than very dull on any test at any age. Sixteen children are considered border-line defective in school (T.M.L. 70-79); 12 of these were rated at this level or lower from 6 months; no child scored higher than very dull at any examination after 2 years. Fourteen children are rated as very dull and will need adjustment help or retardation in class; at 6 months 10 scored at this level or lower; only two children were considered to have a D.Q. above 95 at 3 and 4 years.

TABLE 2

CORRELATION COEFFICIENTS BETWEEN T.M.L. SCORES AND D.Q. SCORES AT DIFFERENT AGES

Age	Correlation Coefficient	No. of Cases
6 months	0·54	237
1 year	0·57	240
2 years	0·66	234
3 years	0·78	192
4 years	0·82	171

All authorities agree that the early assessment of superior ability is much less accurate. To date, 60 children have scored 115 or higher on the T.M.L. test. Of these, 11 were 4½ lb. or less at birth, 14 between 4½ and 5½ lb., and 35 over 5½ lb. Fig. 2 shows pre-school assessments for these superior children at ages from 6 months to 4 years, by birth weight. In the smallest birth weight group over 60% were rated as low average or below at 6 months. Some of them were considered quite markedly retarded, but at each subsequent examination the number of below average children decreased. At 4 years one child was considered average and 10 above average. Most of these children came from middle-class homes, and the rest from superior working-class homes. In the mature control group one-half of the children were rated as above average at 6 months, and three-quarters by 3 years. At 3 and 4 years three children were considered below average on test responses, all of them coming from very poor homes with restricted opportunities.

In attempting to predict future ability in the pre-school period it is necessary to take full cognisance of birth weight, degree of opportunity available to the child, and any handicapping features in the environ-

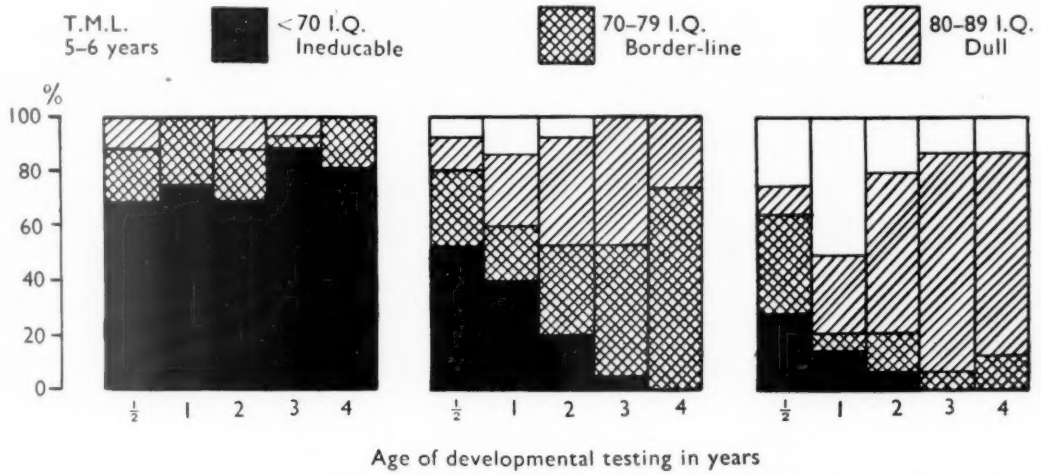

FIG. 1.—Pre-school assessments on developmental testing in children considered ineducable, border-line defective, and dull in the first year in school.

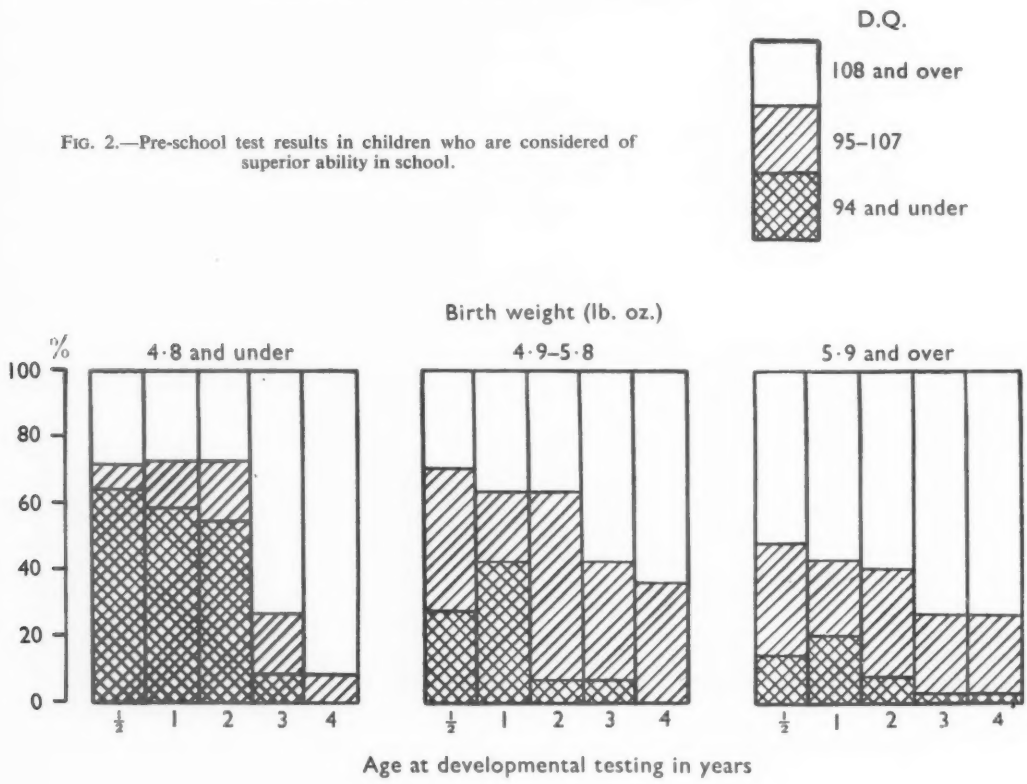

FIG. 2.—Pre-school test results in children who are considered of superior ability in school.

ment. Experience from this group indicates that retarded children who will later prove to be ineducable in normal school should be recognizable by 1 year, and nearly all border-line or very dull children by 2 years. A number of children, mainly small prematures, who subsequently proved to be of average or superior ability in school, were rated at equally low levels at 6 months, and came under close observation for this reason. Nearly all showed obvious improvement at 1 year, and all showed progressive improvement after this age. In cases of suspected retardation the trend of development is of greater importance than the actual score at any one age. The early detection of mental retardation is the most important function of developmental testing, the prediction of average or above average ability being mainly of academic interest. Nevertheless, if those factors in the child's life experience which may affect development are known, it should be possible to reach a quite high degree of accuracy in predicting future ability in fairly broad groupings by the age of 2 or 3 years.

A comprehensive commentary on the recent literature about the predictive value of early developmental testing is given by Illingworth (1960) in a recent book. He stresses the importance of considering the child and his environment as a whole, of assessing not only the child's ability to perform a certain act but the maturity of his response, and the danger of relying on a single examination instead of assessing rate of development. Illingworth concludes that early developmental testing is of great value in the detection of mental retardation and neurological conditions with a considerable degree of certainty, though he has found little evidence that mental superiority can be detected in infancy.

Developmental Ability in Different Birth Weight Groups

Tables 3 and 4 give figures for mean D.Q. at ages 3 and 4 years, and mean score at 5 plus years on the T.M.L. test for singletons and twins in four birth weight groups.

Testing was inadequate, and no score allotted for 17% of singletons at 3 years and 26% at 4 years, and for 37% of twins at both ages. In 10% of singletons and 19% of twins no score was allotted at either 3 or 4 years. This was as often due to the attitude of the mother as it was to lack of co-operation from the child. Failure to make an accurate assessment was more common for mature controls,

and in the poorest homes; but from results of M.L. testing in school it appears that there is little difference between mean scores of children of like birth weight and social grade who were or were not tested at 3 to 4 years.

As at 2 years there is still an obvious difference in mean score between the premature groups and the mature control group. The difference by birth weight is approximately the same as it was at 2 years. Again, twins score lower than singletons of like birth weight at each age. Fig. 3 shows the proportion of children in the four birth weight groups who come into the broader categories given above. The increase in dull, retarded and defective children as birth weight decreases is still very obvious at 4 years.

Developmental Ability by Birth Weight and Maternal Grade

In the 2-year analysis it was found that developmental ability was related both to birth weight and grade of mother, the difference between children from the best and worst homes being greatest for those who were smallest at birth. This difference by social grade is still obvious at 3, 4, and 5 plus years, as shown in Table 5. The difference in mean D.Q. at 4 years for children from the best and worst homes is 32 points for those who were 3½ lb. or less at birth (the difference was 17 points at 2 years) and nine points for those who were over 5½ lb. at birth. The mean score at 3 to 4 years for the mature controls in the best maternal grade group is likely to be an underestimate, owing to the difficulty

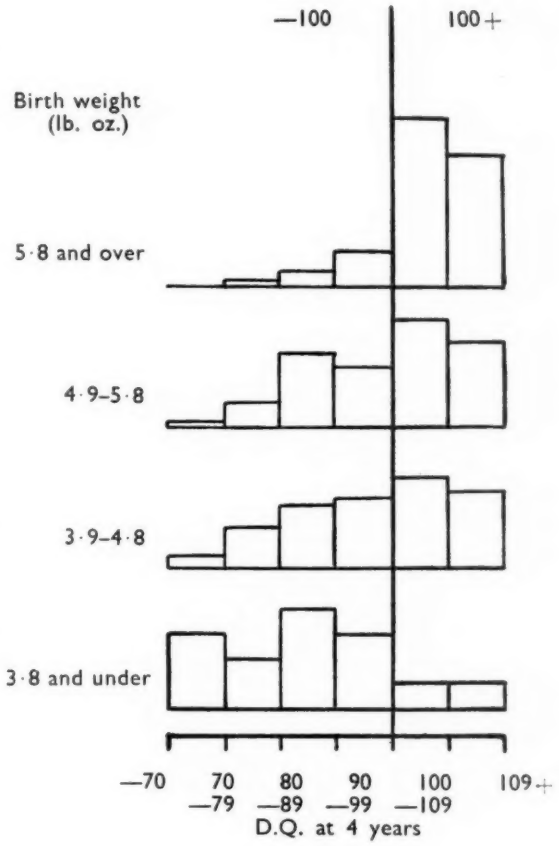

FIG. 3.—D.Q. groups at 4 years by birth weight.

TABLE 3
MEAN SCORES ON INTELLIGENCE TESTING BY BIRTH WEIGHT (SINGLETONS)

Birth Weight	3 years			4 years			5+ years	
	No. of Cases	No. Tested	Mean D.Q.	No. of Cases	No. Tested	Mean D.Q.	No. of Cases	Mean I.Q.
(1) 3 lb. 8 oz. and under ..	38	34	84·5	36	30	82·5	17	76·9
(2) 3 lb. 9 oz.–4 lb. 8 oz. ..	57	52	95·3	57	52	97·2	23	100·8
(3) 4 lb. 9 oz.–5 lb. 8 oz. ..	136	109	99·6	133	89	100·1	78	102·1
(4) 5 lb. 9 oz. and over ..	111	90	106·8	108	77	108·7	59	113·1
Difference 4–1			22·3			26·2		36·2

TABLE 4
MEAN SCORES ON INTELLIGENCE TESTING BY BIRTH WEIGHT (TWINS)

Birth Weight	3 years			4 years			5+ years	
	No. of Cases	No. Tested	Mean D.Q.	No. of Cases	No. Tested	Mean D.Q.	No. of Cases	Mean I.Q.
(1) 3 lb. 8 oz. and under ..	12	9	74·2	12	10	73·3	9	73·4
(2) 3 lb. 9 oz.–4 lb. 8 oz. ..	41	29	93·2	41	25	95·9	22	99·1
(3) 4 lb. 9 oz.–5 lb. 8 oz. ..	58	36	95·9	57	34	97·0	14	99·2
(4) 5 lb. 9 oz. and over ..	78	45	102·6	78	49	103·5	23	106·3
Difference 4–1			28·4			30·2		32·9

TABLE 5

MEAN SCORES ON INTELLIGENCE TESTING AT DIFFERENT AGES BY BIRTH WEIGHT AND MATERNAL GRADE

Maternal Grade	Age (years)	Birth Weight			
		3 lb. 8 oz. and under	3 lb. 9 oz.–4 lb. 8 oz.	4 lb. 9 oz.–5 lb. 8 oz.	5 lb. 9 oz. and over
1 and 2 Middle class and superior working class	3	98	101	102	108
	4	100	102	104	110
	5+	104	112	110	118
3 Average working class	3	80	92	99	103
	4	73	93	101	103
	5+	74	93	104	106
4 Poor working class	3	66	80	93	97
	4	64	84	88	98
	5+	59	87	93	95

previously mentioned of assessing children of superior ability. On T.M.L. scores there is a mean difference of 45 points of I.Q. between children from the best and worst homes who were 3½ lb. or less at birth, and 23 points for those who were mature controls.

Within each maternal grade group mean D.Q. increases with increasing birth weight, but the effect of small birth weight is much more marked in those from the poorest homes. In maternal grade groups 3 and 4 there is little difference in mean score between those prematures who were over 4½ lb. at birth and the mature controls. Many of these so-called prematures are small babies born at or near term to small mothers, often of poor physique. Children from the best homes who were this weight at birth do score significantly lower. More of these children were premature by gestation time as well as by birth weight. Fig. 4 shows the same data arranged in a different way, for children from the best homes, and gives the proportion, by birth weight at 4 years, who were considered (1) defective (D.Q. <70); (2) border-line (D.Q. 70-79); (3) dull (D.Q. 80-89); (4) low average (D.Q. 90-99); (5) average or good average (D.Q. 100-109), and (6) superior (D.Q. 110 and over). Even in the best environment the proportion of children considered below average at 4 years increases markedly with decreasing birth weight although there are very few dull and retarded children in this group as compared with those of like birth weight from poorer homes. However, it should be remembered that an I.Q. of 100 in a child from a professional home with parents of superior ability may indicate as marked a degree of retardation as an I.Q. of 75 in a child from a poor home with parents of low intelligence. In a statistical analysis the former is considered normal, while the latter rates as a border-line defective.

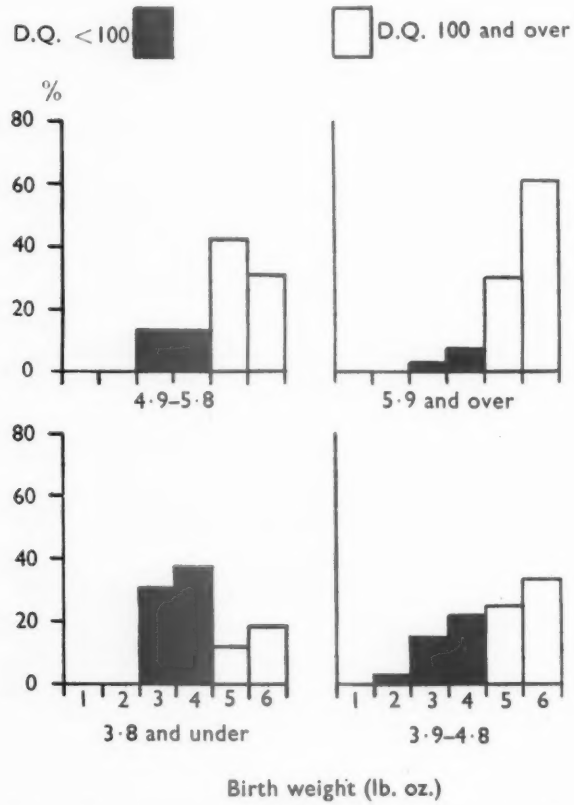

FIG. 4.—Developmental gradings by birth weight—maternal grades 1 and 2.

Discussion

From the close personal observation of this group of children, their homes and families over 4 to 5 years, it appears that mental development, so far as this is measurable by developmental history, intelligence testing, and observed behaviour, is affected by birth weight, genetic endowment, and environment of upbringing.

Prematurely born children from the best homes with parents of above average intelligence show

a steady improvement from 6 months, which is most marked in the first two years of life. Children from the poorest homes show a lesser improvement on average up to 18 months or 2 years, and thereafter those who appear to be retarded tend to deteriorate further. A number of longitudinal studies of development in children of different birth weight are at present in progress. In this country the most comprehensive is the inquiry into later development of a representative group of premature children and full-term matched controls provided by the Maternity Survey of 1946 (Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee, 1948). These children have now passed into secondary school. An assessment of mental ability was made at 2½ years (Douglas, 1956b), at 8 years (Douglas, 1956a), and at 11 years 3 months (Douglas, 1960). Although Douglas states in his most recent paper (1960) that the apparent retardation in walking and talking amongst prematures could be satisfactorily explained when the ages of both prematures and matures were calculated from conception, little weight can be attached to an assessment of early ability based on a brief history given to a health visitor when the child was 2½ years old. However, at 8 years over 80% of surviving children completed a series of standardized tests. The average score for prematures was between 1·7 and 3·0 points lower than that for controls, on a test with a mean for the whole group of 50 and standard deviation of 10. At 8 years environmental differences were considered minimal because of the matching of controls, and were not thought to account for differences in mental ability. At 11 years bigger differences were found on test scores, ranging from 3·0 to 4·2 points. Moreover, only 9·7% of prematures gained entrance to grammar school, as compared with 22·0% of controls. A reappraisal of environment revealed that certain differences existed between the premature and control groups which had hitherto been disregarded, particularly in the social and educational background of parents, and in their interest in and standards of care of their children. In conclusion, Douglas states: 'In a national study of the mental ability and primary school progress of premature children a number of striking handicaps were found, which were later shown to be of environmental origin, rather than the result of low birth weight *per se*.' One would not expect to find big differences between prematures and controls in Douglas's sample. The majority of the children selected were between 4½ and 5½ lb. at birth, and many of these were small babies born at or near term. Less than 10% of the entire group were 4 lb. or less at birth. In the Edinburgh group little difference was found between premature children over 4½ lb. and mature controls in working-class homes. In middle-class families some difference was evident, but more of these children were premature by gestation as well as birth weight. Differences in average score of the order of three to four points might be explained on the basis of the environmental differences noticed. However, when the distribution of scores between the two groups is examined (Table 6), more important differences are found. Assuming that the mean test score of 50 approximates to an I.Q. of 100, children scoring less than 40 would be considered definitely backward, those between 40 and 44 as dull, 45 to 54 average, and 55 and over above average. There are nearly twice as many above average children in the control group, and less than one-half the number of retarded children. It seems unlikely that such a marked excess of very dull or retarded children could be explained by such environmental differences as 6·5 and 3·5% paternal unemployment, or 24·7 and 17·6% previous attendance by fathers at night school. One might equally well postulate that the superiority of children whose fathers had attended night school was genetically determined. In the Baltimore study (Harper, Fischer and Rider, 1959; see Table 7) the

TABLE 6

PROPORTION OF PREMATURE AND MATURELY BORN CHILDREN IN DIFFERENT INTELLIGENCE GROUPINGS AT 11 YEARS: 618 CASES
(Constructed from Douglas, 1960)

Score	Premature %	Mature %
<40	21	9
40–44	15	17
45–54	39	40
55 and over	16	29
Unknown	9	5

TABLE 7

PROPORTION OF PREMATURE AND MATURELY BORN CHILDREN IN DIFFERENT INTELLIGENCE GROUPINGS AT 3–5 YEARS: 900 CASES
(Constructed from Harper *et al.*, 1959)

Mental Grade	Birth Weight (g.)		
	1,500 or less	2,001–2,500	2,501 or more
White:			
Defective	17·7	7·4	3·5
Dull or low average ..	17·6	15·0	10·6
Average	47·1	46·3	44·7
Above average ..	17·7	31·3	41·1
Non-white:			
Defective	27·0	11·0	6·6
Dull or low average ..	45·9	41·5	37·4
Average	27·0	41·0	43·2
Above average ..	—	6·5	12·8

incidence of defective children is over four times as high in the smallest premature group as in the matched control group. In this study more detailed social indices were employed in matching than in Douglas's group, including some details of the parents' social background before marriage. Though there may still be some residual differences in environment between the two groups, it is unlikely that this could account for more than a small part of the differences in mental level observed.

Summary

The mental development of a group of over 500 singletons and twins of different birth weight has been studied at 3 and 4 years. About half the group have entered school, and results of intelligence testing between 5 and 6 years are available. The following conclusions were reached.

As at 2 years mean scores on intelligence testing fall steadily with decreasing birth weight at 3, 4 and 5 years. Twins show consistently lower scores than singletons of like birth weight. At 4 and 5 years there is a striking excess in the smaller premature groups (i.e. 4½ lb. or less) of children who are ineducable in normal school, or will need special educational treatment within the normal school.

Mental development is related to the apparent intelligence of the mother and to the type of home. Differences between social grades appear to be greater at 4 and 5 years than at 2 years. In average and poor working-class homes there is little difference in mental ability between those prematures who were over 4½ lb. at birth and mature controls. In superior working-class and middle-class homes the child who was between 4½ and 5½ lb. at birth is still at a disadvantage. Most of these children were premature by gestation as well as by birth weight.

The predictive value of early developmental testing is discussed, and correlations given between D.Q. scores at ages 6 months to 4 years, and score on the Terman-Merrill L form test at 5 to 6 years. The expected response to pre-school developmental tests is affected by birth weight, environment and opportunity. Early developmental testing is of most value in the detection of children who later prove to be dull, retarded or defective.

I am indebted to Miss A. T. Paterson, Principal Educational Psychologist, and her Staff at the Edinburgh Corporation Education Department Child Guidance Centre, who have undertaken the intelligence testing of children in Edinburgh Corporation Schools; and also to Professor R. W. B. Ellis for his interest and encouragement throughout.

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NORMAL HEAD GROWTH AND THE PREDICTION OF HEAD SIZE IN INFANTILE HYDROCEPHALUS

BY

EILEEN M. O'NEILL

From the Department of Paediatrics, City General Hospital, Sheffield

(RECEIVED FOR PUBLICATION OCTOBER 24, 1960)

PART I

Normal Standards of Head Size and Growth in Full-term and Premature Babies

The earliest possible detection of progressive infantile hydrocephalus requires more detailed standards of normal head size and growth than any previously published. The first part of this communication has been prepared with the object of providing such standards for both full-term and premature babies.

There are two distinct ways of collecting growth data. When values are obtained from *different* children at different ages, no child having been measured more than once, the study is said to be cross-sectional and the values obtained from it provide only *distance* standards. This means that they can be used only for assessing size achieved by a certain age. If increments of growth (velocity standards) are required they should, according to Tanner (1952), be obtained from longitudinal (or serial) studies in which the *same* children are followed up and measured at different ages. In fact most growth studies are not purely of one type or the other.

With regard to head size in newborn babies, distance standards available in this country are inadequate in that in none of the published series is head size related to birth weight, whereas the range of normal head circumference for a small infant is quite different from that of a larger one. After the first few days of life *actual* head size is overshadowed by the far more important *rate* of head growth, normals for which we have already seen must be obtained from longitudinal studies. Before 1952, all surveys of infantile head size on British children were of the cross-sectional type, an example of which is that of Myers (1926) in which measurements were taken from 1,400 London children.

Since 1952, results of three longitudinal surveys of head growth of British children have been published (Low, 1952; Westropp and Barber, 1956; Falkner, 1958) and all, therefore, are suitable for calculating normal velocity standards. Low (1952) recorded head circumference values at 3 days of age and then at yearly intervals. Westropp and Barber (1956) made more frequent measurements on the 331 boys and 333 girls of their series. The heads of these children were measured at 1 month, 3 months, 6 months, 9 months and 1 year, and thereafter at half-yearly intervals up to 7 years. In Falkner's (1958) survey the data were obtained at 4, 13, 26, 39 and 52 weeks of age and then at less frequent intervals up to 3 years. These studies, however, are inadequate for the *early* detection of abnormal rates of head growth because the units of time for which the increments of growth can be or have been calculated are so great that, if they are used, the diagnosis of progressive hydrocephalus must be very much delayed.

No mention has so far been made of the normal head circumference values of premature babies, and the only references to such measurements in the literature are those of Crosse (1957) and Anderson (1950). Only in the latter was the range of normal given and both were almost certainly from cross-sectional data.

To summarize, then, it was felt that there was a definite need for detailed longitudinal studies of head growth in both full-term and premature babies. Such a survey was embarked upon with the object of obtaining data suitable for assessing the head size of all babies at birth and rates of head growth at intervals of one or two weeks, as only by these means could treatment for progressive hydrocephalus be instituted early enough to be successful.

Material

The babies included in this survey were white children born either in the Maternity Unit of the City General

Hospital, Sheffield, or St. Helen Hospital, Barnsley. A small minority was born at home and admitted shortly after birth because of low birth weight. The infants chosen were (1) all those of 5 lb. 8 oz. and under at birth, and (2) all those with birth weights of more than 5 lb. 8 oz. whose mothers would be able to attend with them at one of the three largest Infant Welfare Clinics in Sheffield, or one of the two largest clinics in Barnsley. The object of the survey was explained to all the mothers of these two groups and those cases were excluded in which either parent did not wish their child to take part.

Method

On each occasion the measurement taken was the maximum head circumference which, in view of the wide variations of head shape, was not constantly related to any fixed bony points. To obtain this measurement the baby was placed and held on one or other side and then the tape measure was placed round the widest part of the head, care being taken not to kink the tape or fix it in the wrong plane between the couch and the most dependent part of the baby's head. All measurements were taken to the nearest 0·1 of a centimetre with the tape unstretched but with all the slack taken up. At least three measurements were taken to ensure that the maximum circumference was being measured and the largest constant value was recorded, together with the body weight (unclothed) and the date, on a separate card for each infant. The measurement on each occasion was taken without reference to the previous one, and the result was written down immediately to avoid error. It became obvious very early in the survey that this strict routine had to be adhered to in order to avoid large errors. I took all measurements using a narrow linen tape which had been checked for accuracy before use against a centimetre scale. The tape was checked periodically against this standard and was discarded when it had stretched 0·5 mm. per 10 cm.

The first measurement was taken as soon after birth as possible, usually within the first 24 hours. A small minority was not measured until 2 days old. A second measurement was taken at 7 days old ± 1 day, and a third at 2 weeks ± 2 days, in those cases still in hospital. The vast majority of full-term infants, however, had been discharged from the Maternity Units before the third measurement could be taken. All the mothers, before discharge from hospital, were given an appointment to attend with the baby at the appropriate Welfare Clinic within seven to 13 days of going home. The aim was to obtain weekly measurements up to the age of 5 weeks and fortnightly measurements thereafter at 7, 9, 11, 13, 15 and 17 weeks of age, ± half a week. This pattern was followed well in some cases, but in others, mainly through defaulting and partly due to the hiatus between the last measurement in hospital and the first clinic attendance, this timing was lost. In these cases, some of the measurements were taken on 'even weeks' of age. Finally, because so many fell into this group all measurements were related to the nearest week of age, and placed in weekly groups.

Those babies nursed in the Premature Baby Units had head circumference measurements taken in the same way as the full-term babies as soon after birth as possible and then at weekly intervals (±one day) until discharged from the Unit. Because many of the babies were quite small and had a hospital stay of relatively long duration, regular weekly measurements presented no difficulties. After discharge from the Unit appointments were made to see the babies at the City General Hospital Premature Baby Clinic and in some cases at the local Infant Welfare Centre. From this time onwards the same difficulties of lack of regular clinic attendance were encountered as in the full-term babies. In the case of premature babies head measurements were taken at the clinics as frequently as possible (usually fortnightly) up to 26 weeks of age, and, as before, were finally divided into age groups of multiples of one week ± half a week.

As expected, the attendance at clinics was variable; some mothers brought their babies regularly for the required length of time and others failed to attend at all. Between these extremes were those who came regularly but for short periods of time and others who attended sporadically. Table 1 shows these cases divided into groups according to the length of time of follow-up.

TABLE 1
NORMAL HEAD CIRCUMFERENCE SURVEY
Time of Follow-up—All Cases

Time of Follow-up	Cases	
	Full-term Babies	Premature Babies
Birth only	45	29
Birth to 1 week	181	12
Birth to 2 weeks	45	14
Birth to 3 weeks	35	20
Birth to 4 weeks	38	8
Birth to 5 weeks	35	11
Birth to 6 weeks	24	14
Birth to 7 weeks	26	5
Birth to 8 weeks	23	7
Birth to 9 weeks	21	3
Birth to 10 weeks	15	5
Birth to 11 weeks	11	1
Birth to 12 weeks	18	4
Birth to 13 weeks	20	25
Birth to 14 weeks	9	7
Birth to 15 weeks	8	5
Birth to 16 weeks	8	2
Birth to 17 weeks	23	2
Birth to 18 weeks	51	1
Birth to 19 weeks	21	2
Birth to 20 weeks	19	0
Birth to 21 weeks	—	2
Birth to 22 weeks	—	3
Birth to 23 weeks	—	1
Birth to 24 weeks	—	0
Birth to 25 weeks	—	4
Birth to 26 weeks	—	38
Total	676	+225=901

The survey of full-term infants lasted eight months and of premature infants 13 months. During that time 3,235 and 1,404 head circumference measurements were taken from the 676 and 225 full-term and premature babies respectively. In all, therefore, 901 male and female babies were involved in the survey and a total of 4,639 normal head circumference measurements was made.

Results

The material collected in the above manner was presented to Dr. G. H. Jowett of the Department of Statistics, Sheffield University, and he and his assistant, Mrs. W. Wright, kindly analysed it. With the measurements went a request for the following items and charts:

1. A head circumference/age chart for *full-term* infants during the first *three* months of life.
2. A head circumference/age chart for *premature* babies during the first *six* months of life.
3. A chart to show the normal range of head circumference at birth related to birth weight, this chart to include both premature and full-term infants.
4. The normal range of increments of head circumference in premature and full-term infants, with special emphasis on details in the first weeks of life and with a view to the earliest possible diagnosis of deviations from the normal.

These will now be reported under their appropriate headings.

(1) Head Circumference/Age Chart for Full-term Infants.* This is reproduced in Fig. 1. It should be noted that in this and the other graphs of this report the boys' measurements have not been separated from those of the girls.

The curves were constructed by plotting the head circumference values from the record cards against age. From the scatter diagram so produced horizontal and vertical means were obtained; these were joined by eye and resulted in the mean curve. Histograms of deviations from the mean were constructed and from these the 2·5 and 97·5 percentiles were derived.

Unlike Westropp and Barber's (1956) and Falkner's (1958) results, those of the present series were detailed enough to demonstrate the relatively steep rise in head circumference found in the first six to eight weeks of life. From this time onwards the curves are very similar in all these charts, but those resulting from the present study show a narrower range, although they are comparable to those of Westropp and Barber (1956) and Falkner (1958) in that they represent 95% of the series. This difference probably lies in the fact that all the measurements of the present series were taken by one individual and that the values obtained were more closely related to the specified ages.

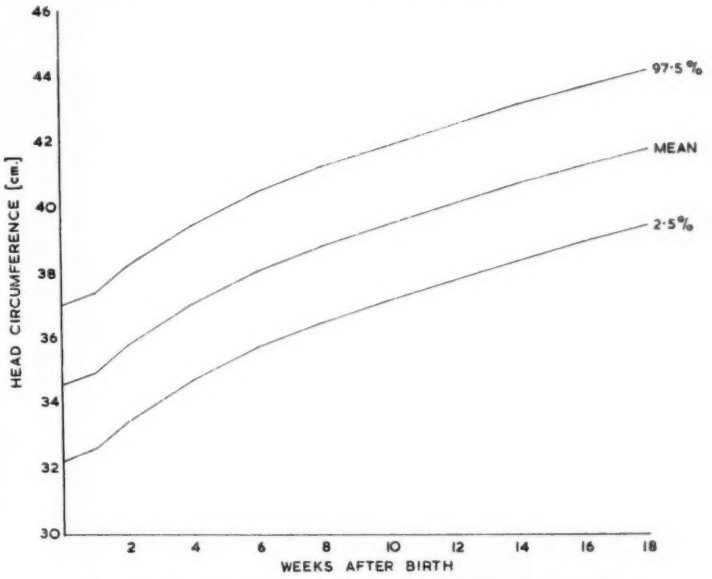

FIG. 1.—Head circumference/age chart for full-term babies; 95% limits for head circumference with respect to age.

(2) Head Circumference/Age Chart for Premature Infants. The method of construction of this graph was exactly the same as for the full-term infants and the result is shown in Fig. 2. It should be noted that the curve representing the mean value is not centrally placed; this was presumably due to 'weighting' of the results with a larger proportion of big babies to small as would be expected in a survey of premature infants.

Fig. 3, which consists of the graphs of Figs. 1 and 2 superimposed, has been drawn to show the striking difference between the normal ranges of head circumference in full-term and premature babies. When seen in this way it is obvious how ridiculous it is to try and assess the head size of a premature infant by comparison with normal full-term standards.

(3) Chart to Show Normal Range of Head Circumference at Birth Relative to Birth Weight. Such a chart (Fig. 4) was constructed in a manner similar to the previous two, but in this case the head circumference values were plotted against birth weight and the curve was fitted to the means by 'least squares' instead of by eye. The graph covers a weight range from 3 to 9 lb. at birth. The curves are based on the maximum head circumference at

* The actual values used for the construction of graphs described in this report can be obtained on application to the author.

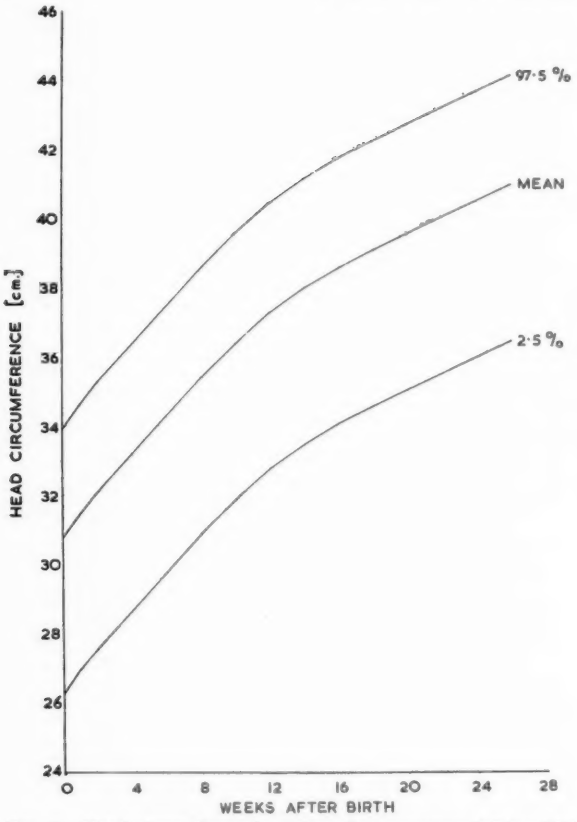

FIG. 2.—Head circumference/age chart for premature babies; 95% limits for head circumference with respect to age.

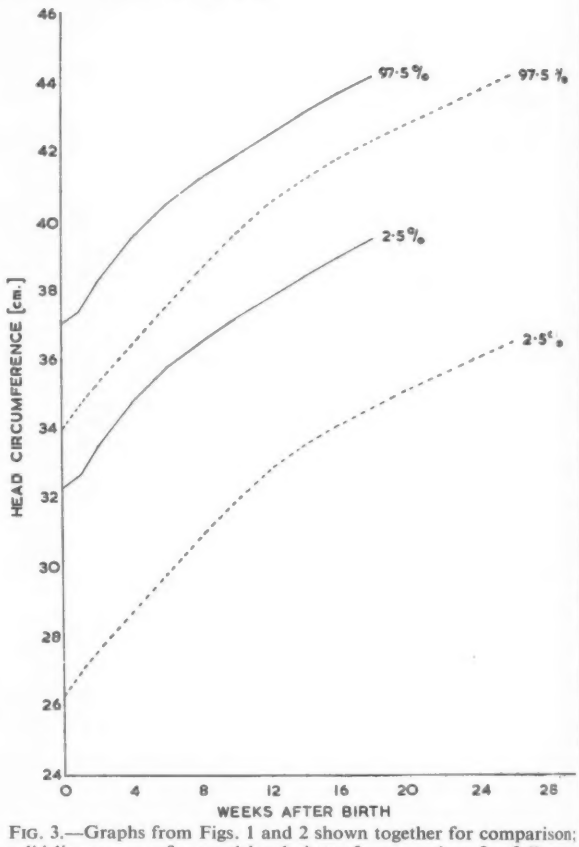

FIG. 3.—Graphs from Figs. 1 and 2 shown together for comparison: solid line: range of normal head circumference values for full-term infants; broken line: range of normal head circumference values for premature infants.

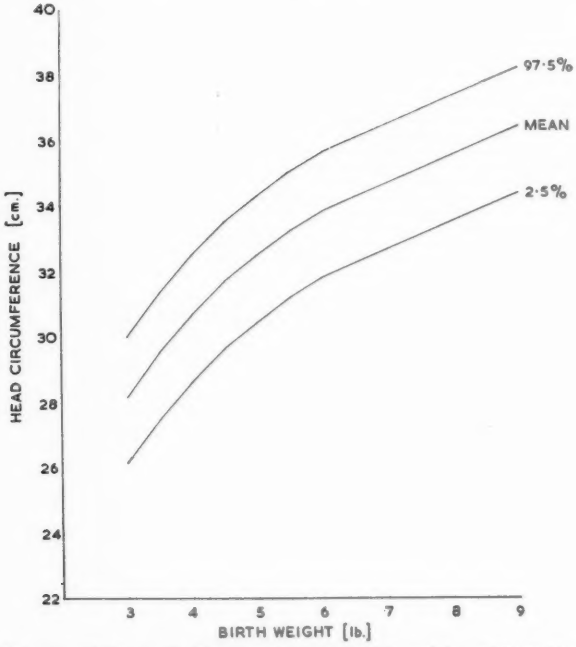

FIG. 4.—Head circumference relative to birth weight; 95% limits for head circumference at the first week relative to birth weight.

1 week of age, plus or minus one day, rather than on the measurements taken within the first two days of life. This is because moulding, caput formation and/or oedema of the scalp may result in gross changes in the head measurements in the first few days of life, so making those taken at 1 week the most reliable first measurement, which for all practical purposes can be regarded as the head circumference at birth. As with the previous charts, the range given covers 95% of normals.

(4) Normal Range of Increments of Head Circumference in Premature and Full-term Infants. The simplest method of diagnosing progressively abnormal head enlargement is by comparing increments of head growth with a normal range, and when the aim is the earliest possible diagnosis of advancing hydrocephalus these comparisons must be made no less frequently than at weekly intervals. As the rate of head growth is not constant the range of normal increments must be known for each week of age and at least two sets of figures, i.e. one for

premature and one for full-term babies, should be available. Such charts would be useful but clumsy and, unfortunately, would involve the comparative use of small linear measurements so that the error would be relatively high. Also, any weekly increment of head increase could be judged as normal or abnormal but would show no relationship to previous values. To overcome these disadvantages, Dr. G. H. Jowett suggested that probably the best way to demonstrate deviations from the normal would be by the use of 'control lines' and a ratio chart. These will now be described in detail.

(*a*) CONTROL LINES. To understand the significance of these lines it is necessary to know how they were constructed. For ease of description the age of 10 weeks will be taken as an example. The first step was to assume that all the normal head circumference measurements taken from the full-term babies at the age of 10 weeks were superimposed upon a point X. This point (see Fig. 5) was made in a convenient position, unrelated to any fixed point on the ordinate but vertically above the 10-week mark on the abscissa. The measurements on the same children, obtained between 10 weeks and birth, were then plotted backwards from point X, using a 'sliding' logarithmic centimetre scale as the ordinate. (The reason for using a logarithmic scale will be explained under the next heading.) The points for each individual child were then joined and the result was a series of backwardly diverging lines, as shown in Fig. 5, the upper and lower limits of which represent the minimum and maximum *rates of increase* in head circumference in this group of normal infants. Any obviously stray line was disregarded when drawing the final boundaries separating normal from abnormal.

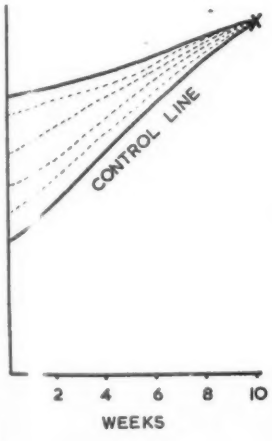

FIG. 5.—Diagram to demonstrate construction of control lines. The two heavy lines diverging backwards from X mark the limits of normal; the *upper one* represents the *minimum* rate of increase in head circumference and the *lower one* the *maximum* rate of increase in head circumference consistent with normality. In the present context the latter is known as the control line. In the diagram the control line for the 10th week is represented.

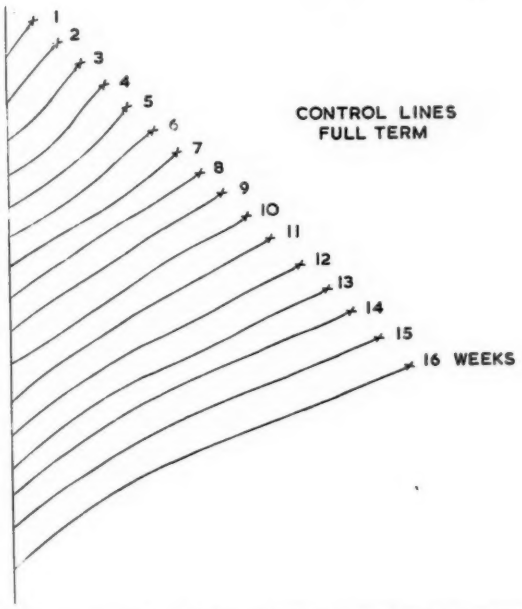

FIG. 6.—Control lines: full-term infants. Each line represents the maximum normal rate of increase in head circumference from birth to the week of age indicated by the number at the end of the line.

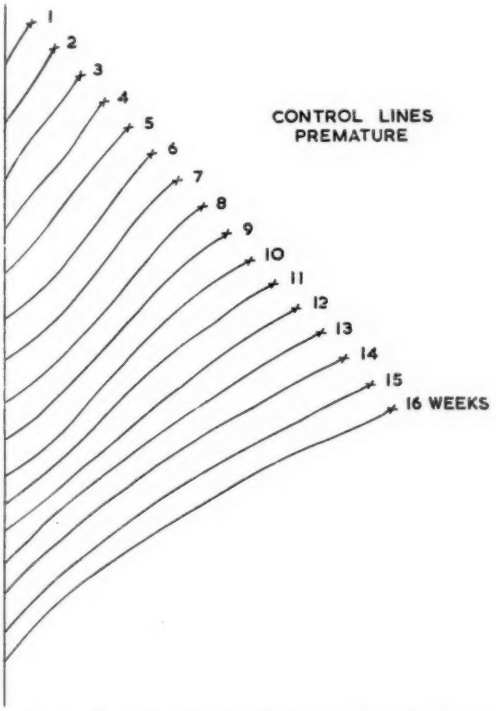

FIG. 7.—Control lines: premature infants. Each line represents the maximum normal rate of increase in head circumference from birth to the week of age indicated by the number at the end of the line.

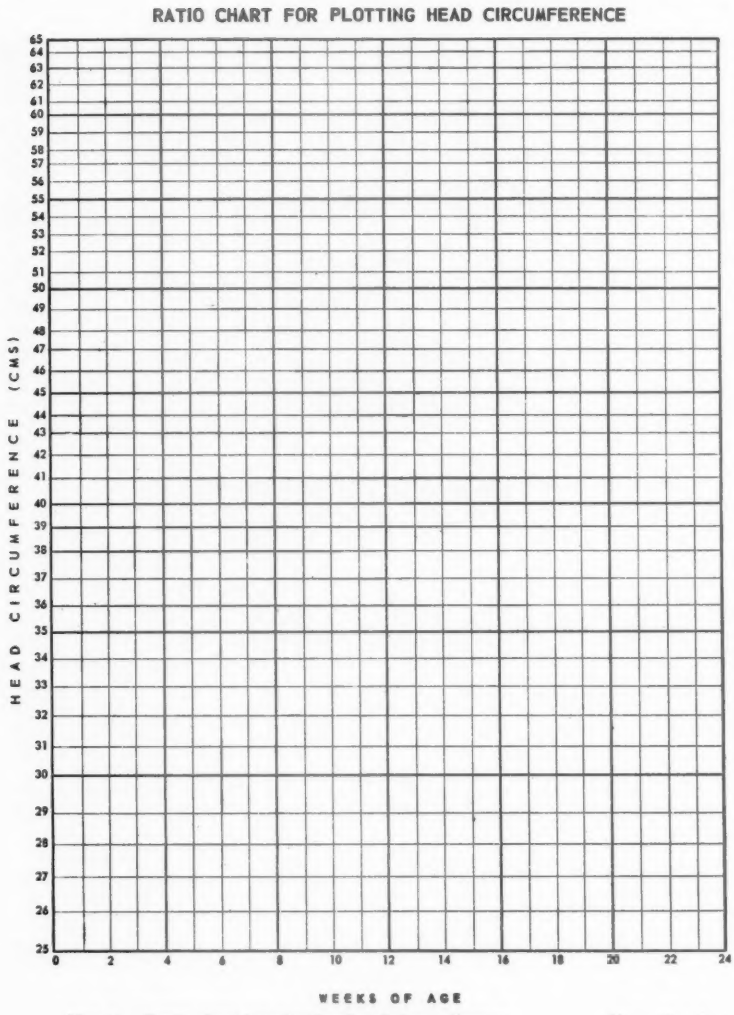

FIG. 8.—Ratio chart for plotting head circumference.

Knowing this construction it is obvious that if any measurements taken from a head which is growing too rapidly are added to Fig. 5 (with the 10th week measurement coinciding with point X) the line produced will be *steeper* than any of the others and hence will lie *below* the normal range. It follows that the lowest of the normal lines represents the *maximum rate of increase*, or steepest gradient, consistent with normality, and it is this line, together with those for all other ages from 1 to 16 weeks, that constitute the 'control lines' previously referred to. This series and a similar one obtained from the premature baby measurements were drawn as two separate charts on transparent paper, the latter being necessary as the use of the control lines involves their superimposition upon a 'ratio chart' which will be described in the next paragraph. The two sets of control lines are shown in Figs. 6 and 7.

(*b*) RATIO CHART. The 'ratio chart' differs from the conventional head circumference/age chart in that the head circumference is plotted as a logarithmic scale in order to obtain, as far as possible, equal significance in the units of head growth of both large and small babies. A centimetre scale was chosen, and this, together with the age in weeks, was drawn on the same scale as the one on which the control lines were constructed. The result is shown in Fig. 8.

(*c*) USE OF RATIO CHART AND CONTROL LINES. To use these charts the head circumference, in centimetres, is first plotted against age on the ratio chart. The control lines are then superimposed on the latter, the ordinates of each graph being placed exactly one above the other as in Fig. 9. The transparency is then moved vertically up or down, still keeping the ordinates exactly matched, until the X at the end of the control line of the appropriate week coincides with the patient's head circumference of the same week. If the head circumference growth curve lies below the control line, in part or in whole, then the rate of head growth has been abnormally rapid and, conversely, if it lies completely above the control line the increments have been normal up to that age.

PART II

Method for Predicting Eventual Head Size in Early Stages of Infantile Hydrocephalus

The second part of this paper leads on naturally from the normal charts, just reported, to their use in the early stages of infantile hydrocephalus.

Either before or after birth there is a stage in the pathology of hydrocephalus in which the ventricles are expanding more rapidly than normal and a stage at which (no doubt through an equalization of pressures) the hydrocephalus arrests (Laurence, 1958). If operation to relieve intraventricular pressure is going to be of value then it clearly should be done during the progressive phase. To begin with, at least, it should *not* be performed in those patients in whom arrest is going to occur

ea·ly and spontaneously in any case. It is therefore im·portant to try and discover which cases will ar·est early and which will arrest late.

Grouping. It is well known that in some children wi·h manifest hydrocephalus the head circumference can still remain within normal limits: in others it can finish just above normal: in others it can become enormous. Arbitrarily, it was decided to call all those with normal head circumferences at the age of 1 year, Group 1: those with eventual head sizes no more than 5 cm. above normal, Group 2 and those eventually above this, Group 3 (see Figs. 11, 12 and 13).

Material

The patients for analysis came from two sources. First there were 116 cases from two general paediatric and maternity units under the care of Drs. M. Eastwood and R. R. Gordon: these consisted of cases of 'pure' hydrocephalus, encephalocele and spina bifida cystica. Fifty-seven of these survived long enough to be put in a definite group. The remaining 42 patients were a similar series under the care of Mr. R. B. Zachary. There were therefore 99 cases available who could be placed in a definite group as previously defined.

The pathology of the 99 cases is shown in Table 2 with their eventual groups. Of the 47 cases who stayed in Group 1 there were several, of course, who had no signs of manifest hydrocephalus at all, but they have been included since any method of predicting head size should be capable of application to strictly normal heads as well as to grossly abnormal ones.

Most of the cases in the series who had spina bifida cystica had this 'repaired' in the first few days or weeks of life, but no operation for the relief of intracranial pressure was undertaken at any time on any patient and even fluid removed for investigations amounted to no more than a few millilitres.

Method

The objective was to be able to decide as early as possible into which group any individual child would eventually fall. By the use of the control lines and ratio chart described in Part I of this paper we can tell whether the head circumference is *increasing more rapidly than normal* but in most cases what we require is a method of telling whether this rapid rate of progression *is going to continue*.

R·te of increase alone is insufficient in predicting

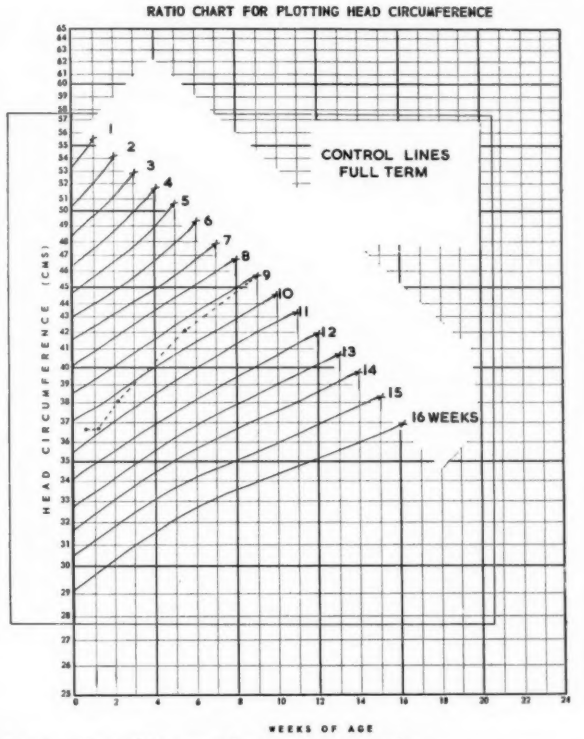

FIG. 9.—Control lines superimposed on a ratio chart. .----.--- .: line joining actual head circumference values. The control lines (for full-term infants) are placed in the position used to assess the rate of head growth at the age of 9 weeks, in a baby weighing 6 lb. 6 oz. at birth. The line joining the head circumference values lies below the 9-week control line and therefore head growth between birth and 9 weeks has been greater than normal.

eventual head size because in some cases of spina bifida cystica the actual head circumference at birth may be smaller than normal (Table 3) so that a considerable increase may not take the circumference out of the Group 1 range.

For this reason in the method to be described the starting point is taken as the actual head circumference at birth or the maximum head circumference for the birth weight (97·5 percentile), whichever is the greater, and this point is marked on the ordinate of the ratio chart at the beginning and is called the *basic point*. The infant's head is then measured once a week and the result is entered on the ratio chart. After recording

TABLE 2
PAT·IOLOGY OF CASES USED FO·R PREDICTING HEAD SIZE

Pathology	Group 1	Group 2	Group 3	Totals
Pure ·ydrocephalus	3	2	11	16
Ence·halocele ..	1	0	1	2
Men·gocele ..	29	5	1	35
Men·gomyelocele ..	14	12	20	46
Totals ..	47	19	33	99

TABLE 3
ALL CASES OF SPINA BIFIDA CYSTICA WITH KNOWN HEAD CIRCUMFERENCE AT BIRTH AND KNOWN BIRTH WEIGHT

Head Circumference Relative to Birth Weight	No. of Cases	Percentage
Above 97·5 percentile	11	17
Within normal range	43	65
Below 2·5 percentile	12	18
Totals	66	100

each weekly measurement the procedure is as follows:

1. Over the ratio chart place the appropriate control lines (full term or premature). The ordinates should match exactly.
2. Move the control lines vertically (keeping the ordinates matched) until the X at the end of the appropriate weekly control line lies over the measurement for that week. It can then be seen if the rate of increase is too rapid.
3. Lay a ruler to join the 'basic point' on the ratio chart to the X of the control line of the week in question. This imaginary line is called the incremental line or line of increment.
4. If the line of increment each week lies above the control line then the head size will remain in Group 1.

   If the line of increment comes to be at any one time *completely* below the control line then the head will finish in Group 3.

   If the line of increment crosses a control line but at no time lies completely below one the eventual head size will be that of Group 2.

   An example showing how Group 3 could be predicted at the age of 3 weeks is demonstrated in Fig. 10.

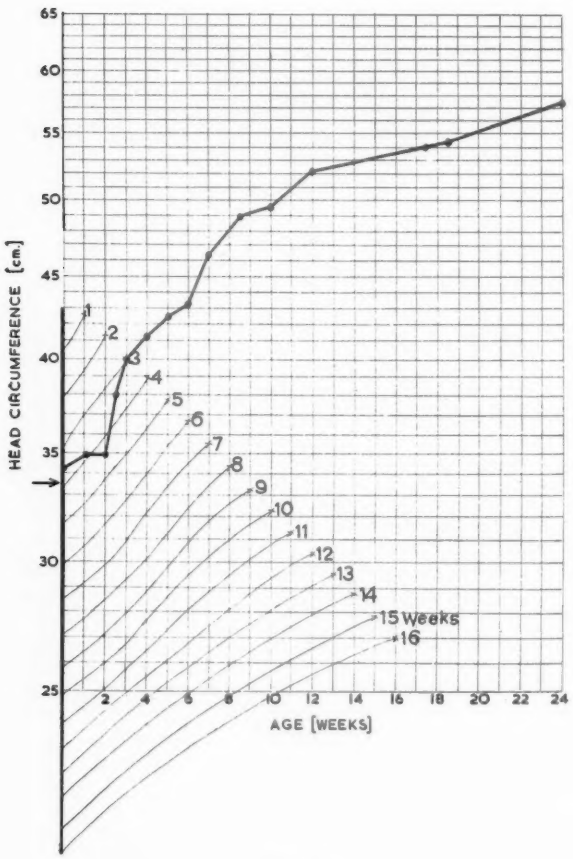

FIG. 10.

Results

Using the method just described in the 99 cases where the final head circumference at 1 year was known accurate predictions could have been made in 90% of them. The percentage accuracy of forecast of the three different groups is shown in Table 4.

TABLE 4
INCIDENCE OF CORRECT PROGNOSIS OF GROUP

	Cases	Predicted Correctly	
		No.	%
Group 1 ..	47	46	98
Group 2 ..	19	12	63
Group 3 ..	33	31	94
Totals ..	99	89	90

As expected, the least accurate group for prediction, when judged alone, is the middle one, but even so more than 60% could have been accurately diagnosed by this method and if one considers Groups 1 and 3 accuracy is as high as 98% and 94% respectively.

This has been a retrospective study but each case has been examined with a view to deciding what the outcome was likely to be and the prediction in each case has been checked against the actual result. By doing this it was found that using this new technique the group, indicating the eventual head size, could be diagnosed in the majority of cases well before the actual head size fell into that group, so that by using this method in future cases any surgery could be carried out well before gross enlargement had taken place. Table 5 shows the findings in the present series expressed in terms of weeks of warning in all cases in whom Groups 2 and 3 were predicted.

There were only 12 Group 2 cases to include in Table 5 and in only five of them was it possible to predict the final group before it was reached;

FIG. 10.—To demonstrate prediction of head size using control lines with a ratio chart. The control lines are numbered from 1 to 16 weeks and are drawn on transparent paper. In the above example they are placed in the position necessary to judge the future outcome for head size had the baby been considered at the age of 3 weeks. The ordinate of the control lines (heavy line) is superimposed on the ordinate of the ratio chart with the X of the control line for the third week coiniciding with the actual head circumference value for the same age. That part of the graph showing head growth from birth to 3 weeks lies below the third week control line so that head growth has exceeded the maximum normal rate during this period of time.

The incremental line is the imaginary line drawn from the basic point to (in this case) the third week measurement. Here it lies wholly below the third week control line so that Group 3 can be expected. This group was reached, in this example, at the age of 7 weeks.

——→ Indicates the 97·5 percentile for head circumference relative to birth weight in this patient.

●——● Actual head circumference values.

TABLE 5
WARNING OF CHANGE OF GROUP

Final Group Reached	Weeks of Warning					Total Cases
	0	1	2	3	4 or More	
Group 2	7*	2	1	0	2	12
Group 3	0	4	2	2	23	31

* One of these was already in Group 2 at birth.

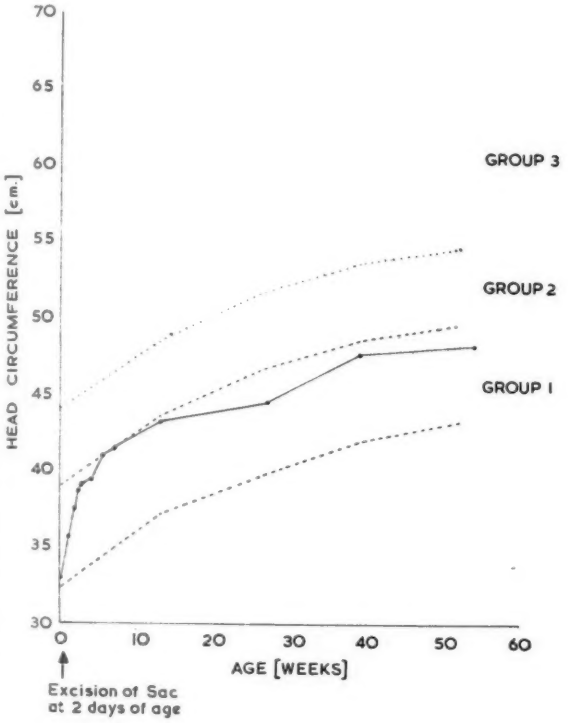

FIG. 11.

FIG. 11.—An example of Group 1 at 1 year of age; Case B.P.; Diagnosis: meningocele, clinical hydrocephalus; birth weight: 6 lb. 14½ oz.

Group 1 = Normal range of head size adapted from Westropp and Barber (1956).

FIG. 12.—Example of Group 2 at 1 year of age. Case L.S.; Diagnosis: meningomyelocele, clinical hydrocephalus; birth weight: 5 lb. 2 oz. Group 1 = Normal range of head size adapted from Westropp and Barber (1956).

FIG. 13.—Example of Group 3 at 1 year of age. Case J.I.; diagnosis: meningomyelocele, clinical hydrocephalus; birth weight 4 lb. 10 oz. Group 1 = Normal range of head size adapted from Westropp and Barber (1956).

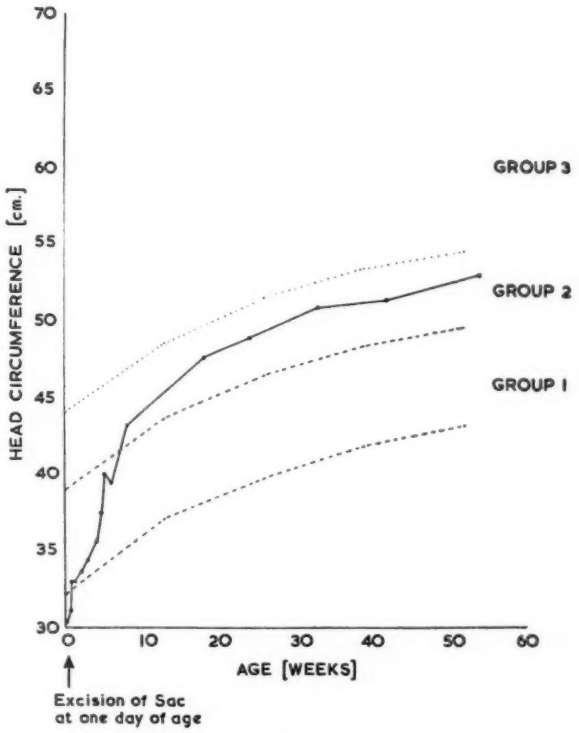

FIG. 12.

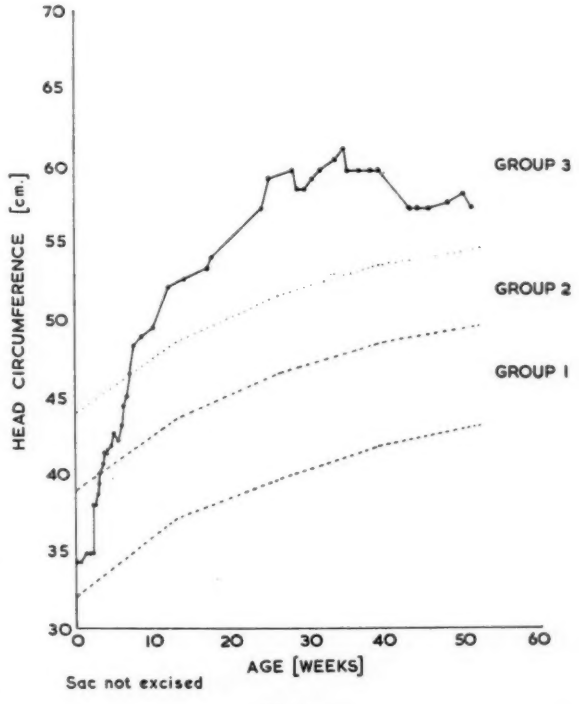

FIG. 13.

the other six cases who showed a rise into Group 2 should not be disregarded because the control lines indicated in each of them that the head size would stay in Group 2, which it did. One case in which the head size was already in the latter group at birth is also included and in this child also the prediction was correct, the rate of increase of head size causing it to stay within the same group. The main interest, however, lies in those cases in Table 5 who eventually reached Group 3. In every single one of them there was at least one week's warning of entry into Group 3 and in 23 out of 31 cases (74%) there were four or more weeks of warning of this happening.

Examples. Three examples are given to demonstrate the value of the new technique (Figs. 11, 12 and 13). It can be seen from their charts (which are ordinary head circumference/age charts amended for grouping purposes) that in all three cases there was a very rapid and comparable increase in head size initially, but eventually as arrest took place the final groups were 1, 2 and 3. Only by the use of the control lines in the way described could the group in each case be accurately forecast *during the stage of progression* and in the Group 3 case this was forecast as early as the third week of life.

DISCUSSION

The survey of normal head growth was undertaken with the object of finding a method whereby the prognosis in the individual case of infantile hydrocephalus could be assessed. Strictly speaking, to detect progressive internal hydrocephalus increases of ventricular volume should be measured, but unfortunately there is no method of doing this which is simple and safe enough for frequent repetition. However, in most cases abnormal growth of the ventricles is reflected in external measurements of the skull and the most informative of these is the maximum head circumference. It was for this reason that the head circumference was chosen for the assessment of normal head size and growth.

Normal Head Size

Many charts are available showing the range of normal head size during the first year of life, but the vast majority of them are from cross-sectional data. It has been and still is common practice to take mean head circumference values from such charts at, say, birth and 12 weeks of age and by subtracting the difference and dividing by 12 calculating the average weekly rate of growth. Even as a rough guide such values can be very misleading. More accurate increments of growth can be obtained from the data of longitudinal studies, but those published so far have not been obtained with the diagnosis of any specific condition in mind and because of this the growth data have not been obtained at frequent enough intervals to reveal the changing growth rate in adequate enough detail. In normal children the greatest rate of change in head size occurs within the first few months of life and it is during this same period of time that the diagnostic and prognostic problems of infantile hydrocephalus arise. It was for this reason that the detailed normal head circumference/age chart for mature babies was only continued up to the age of 18 weeks, but even 16 weeks would have been adequate.

Head growth in premature babies has been neglected in the past. This is rather surprising because these babies have heads which, proportionately to the rest of the body, are larger than those of full-term infants so that the question of hydrocephalus is frequently raised. To eliminate this difficulty and also because the problem of hydrocephalus associated with spina bifida cystica is met in these babies too, the head circumference/age chart for premature babies was constructed from data as detailed as that for the mature infants. Values were obtained up to 26 weeks of age, but for the present purpose only those up to 16 weeks were needed.

Most textbooks quote values of chest circumference and/or crown-rump length as guides to head circumference relative to body size in infancy. The latter especially is difficult to measure with any degree of accuracy under ordinary clinical conditions and both can be very misleading. Although perhaps not the final answer to the problem it was felt that a chart showing the normal range of head size relative to body weight at birth would be useful. This, indeed, has proved to be so, this chart having become vital to the method of predicting head size described in this paper.

Control Lines and Ratio Chart

The control lines described in the first part of this report are graphical representations of rates of head growth and in no way indicate absolute measurements. Their sole function is to provide a boundary between the limits of normality and abnormality in the *rates of increase* of head circumference. Only the boundary indicating the *maximum normal* rate of head growth has been used in the present work. To record these values in numerical form complicated tables would have been needed in order to show a normal range of

growth increments for babies with heads of different sizes. This difficulty was overcome in the present method by constructing separate sets of control lines for premature and full-term babies and by using a logarithmic scale for both the control lines and the ratio charts, so making the same *percentage increases* of head circumference of equal significance. The result is a very simple method of separating the rapid stage of normal head growth from the abnormal rate of growth seen in the early stage of infantile hydrocephalus.

Basic Point and Incremental Line

It has already been mentioned that in one child a very steep gradient of head growth may not necessarily take the head circumference beyond the normal limits of head size, and yet in another the same increment may result in a grossly enlarged head. This, quite obviously, is because of the great variability in head size at birth. Large heads at birth are expected in cases of hydrocephalus, but we have long suspected that some children with spina bifida cystica, who later have manifest hydrocephalus, had abnormally small heads at the start. Even so we were surprised to find that the ones with head circumferences below the 2·5 percentile amounted to almost 20% of the cases with spina bifida. In view of these findings it became obvious that rates of head growth could only be interpreted in terms of future head size, by standardizing the starting point from which increments of growth were to be measured. This resulted in the empirical development of the *basic point*, which has already been defined. In making a prediction of head size, growth is always considered as having taken place from this point so that the line of increment, which is drawn between the basic point and any later head circumference value, represents a standardized rate of growth. In using this method for forecasting, therefore, the curve drawn from the actual head circumference values is ignored and the line of increment only is compared with the control lines. By doing this all the previous difficulties were eliminated and the result was a method of making an individual prognosis for head size, in terms of the three defined groups. This was found to be accurate in 90% of the 99 cases upon whom it was tested.

Fundamental Value of the Method

Previously there has been no method of deciding which children with hydrocephalus will show early arrest and which will progress to the severe condition. Clearly, if any of these cases are to have corrective shunts the time to operate is in the progressive phase and before the head has become abnormally large and brain compression severe. Admittedly, some of these children have normal-sized heads together with gross cortical damage, but these cases are no longer in the progressive phase of hydrocephalus (which may have occurred *in utero*) so that a shunt would be of no use to them in any case. The real value of the method of prediction described here, therefore, is in its capacity to distinguish between what would eventually be mild, moderate and severe cases of hydrocephalus at a time when they cannot normally be distinguished, that is, when they are in the rapidly progressive phase. This is shown readily by the three examples given in Figs. 11, 12 and 13 where a child from each group (Groups 1, 2 and 3) is represented. Each of them showed a very rapidly progressive hydrocephalus, but by the new technique it was possible to anticipate the stage of arrest correctly and in the Group 3 case this prediction was made as early as the third week and whilst the head size was still normal. This quite obviously would have been the optimum time for surgery.

Much emphasis has been placed on the *early* prediction of eventual head size because this is so important if surgery is to aim at maintaining a normal or near normal head size with a minimum of brain damage. In the present series control lines up to the age of 16 weeks were quite adequate for this purpose, in fact, it was found that in 68% of those cases who finally reached Group 3 an accurate prediction of this group could have been given within the first eight weeks of life. It is possible that this may well be related to the fact that the vast majority of cases used for testing this method of prediction were patients with spina bifida cystica and that the patterns of head growth in these children are such that early prediction is possible in most cases. Nevertheless, this is of relatively little significance for in general paediatric practice the majority of cases of infantile hydrocephalus presenting within the first four months of life are associated with spina bifida cystica and hence the method is satisfactory for its requirements. But in any case the technique was also found suitable for forecasting head size in those cases of pure hydrocephalus presenting within the first 16 weeks of life and included in the present series.

Although perhaps the method appears complicated, in fact the use of control lines is simple and easily learnt and only a few minutes is needed on each occasion for working out results. This is important because it means that the required information in each case can be obtained during the out-patient visit and in this way the parents

can be given far more definite answers to their queries and, if surgery is indicated, arrangements for this and the preceding investigations can be made without delay. Such urgency should be appreciated because even one week's hesitation at a stage of very rapid abnormal head growth can result in gross hydrocephalus of the Group 3 grade.

As far as I am aware control lines have never been used before in the medical field. They were adapted for the present purpose by Dr. G. H. Jowett from the ideas of Page (1954) and Barnard (1959) who had previously drawn attention to them and emphasized their value for the inspection and control of industrial processes. Fortunately they are admirably suited to the present piece of work.

SUMMARY

1. A study of maximum head circumference measurements was made on normal full-term and premature babies. The survey was a longitudinal one and all measurements were taken personally. 676 full-term and 225 premature babies were involved and a total of 4,639 measurements was taken from these 901 infants. In the majority of cases head circumference values were obtained at birth and then at weekly and later fortnightly intervals up to 18 and 26 weeks of age from full-term and premature babies respectively.

2. From the material collected in the head circumference survey the following were obtained:

(i) A graph to show the normal range of head circumference in relation to age in full-term infants from birth to 18 weeks.

(ii) A head circumference/age chart to show the normal range of head size in premature babies from birth to 26 weeks of age.

(iii) A chart to show the normal range of head circumference at 1 week of age relative to birth weight. This covered a weight range of 3 to 9 lb. and therefore included premature as well as full-term infants.

(iv) Control lines. These were described with special emphasis on their significance and their use in association with a ratio chart. The 'lines' presented were drawn at weekly intervals from 1 to 16 weeks for both full-term and premature babies. Each control line represents a maximum normal rate of head circumference increase.

3. A method has been described for predicting the head size of any individual at 1 year of age in terms of defined groups. This technique resulted from an empirical modification of the use of control lines and depends on a knowledge of the maximum normal head circumference at birth relative to the birth weight. The predictions are made between birth and 16 weeks of age. The following results emerged from the application of this method to cases in the present series:

(i) An accurate forecast of the Group indicating head size was made in 90% of 99 cases.

(ii) Warning of the impending change of Group was given in just less than half of the Group 2 cases. In three-quarters of the Group 3 patients an accurate prediction of the final head size was made four or more weeks in advance of the change and in the remainder at least one week of warning was given in each case.

4. Three examples, forecast correctly to reach Groups 1, 2 and 3, were given. All three had a very rapidly progressive hydrocephalus, but it was possible during the progressive phase, to distinguish between early, moderately early and late arrest by the technique described in this report.

I wish to thank the Sheffield Regional Hospital Board for the opportunity to carry out this investigation; also Drs. R. R. Gordon, A. Kirk Black and G. A. W. Neill for allowing me to take measurements from children under their care, and Dr. R. R. Gordon, Mr. R. B. Zachary and Dr. M. Eastwood for access to their case notes. I am especially grateful to Dr. G. H. Jowett for the original idea of the control lines and to him and his assistant, Mrs. W. Wright, for constructing them and the head circumference charts from the material obtained during the survey. Finally, I would like to thank Dr. R. R. Gordon for the initial ideas which led to this survey and for his most valuable guidance throughout.

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A STUDY OF RESPIRATORY FUNCTION IN NORMAL SCHOOL CHILDREN

THE PEAK FLOW RATE

BY

JEAN R. NAIRN, A. J. BENNET, J. D. ANDREW and P. MACARTHUR

From the Paediatric Department, Raigmore Hospital, Inverness

(RECEIVED FOR PUBLICATION OCTOBER 4, 1960)

A simple, but reliable, method of measuring the ventilatory function of the lungs has long been sought. With increasing experience of spirometry in clinical medicine it was realized that the measurement of vital capacity is of limited value because the rate of movement of air in and out of the lungs is not taken into account in this test. In 1933, Hermannsen devised the test of maximum breathing capacity (M.B.C.), which does measure this dynamic factor and which, as recently as 1953 (Kennedy) has been considered the best single index of ventilatory function. Unfortunately, it is time consuming, fatiguing for both patient and observer, and is unsuitable for use with seriously ill patients or young children. Several workers have devised tests based on the rate at which air can be forcibly exhaled, usually by measuring, with a spirometer, the volume breathed out during a timed interval of a forced expiration (Roche and Thivollet, 1949; Tiffeneau, Bousser and Drutel, 1949; Kennedy, 1953). These have become standardized as the forced expiratory volume for a stated interval, usually one second ($F.E.V._{1\cdot0}$). This measurement of the rate of respiratory air flow is accepted as a test of respiratory function particularly useful in the study of obstructive airway disease, and gives consistent results in individuals (Strang, 1959; Miller, Johnson and Wu, 1959), and a fairly close correlation with clinical grades of exercise tolerance due to obstructive airway disease (Capel and Smart, 1959). While many instruments are available for measuring the rate of expiratory flow, their size and complexity render them more suitable for use in the laboratory than at the bedside, consulting room or clinic. The anxiety caused in children and even adults by the bulk and appearance of most spirometers, and by the use of nose clips, increases considerably the time required to carry out the test and adds yet another variable to the factors influencing the result.

When the peak flow meter (Wright and McKerrow, 1959), designed for the Pneumoconiosis Unit of the Medical Research Council, became available, it was welcomed by us as a simple instrument, measuring an aspect of ventilatory function similar to that estimated by the F.E.V., and likely to prove of assistance in the assessment of patients, particularly children with obstructive respiratory disorders. In use in the ward, out-patient clinic and school, we have found this instrument robust, portable and easy to use. As with all such instruments, the patient's full co-operation is essential and has been obtained without difficulty from normal children aged 5 years and over. As part of our study it was necessary to establish the peak flow in normal children. It has been shown (Strang, 1959, 1960; Needham, Rogan and McDonald, 1954) that the ventilatory function of normal children varies with age and stature. The peak flow rate (P.F.R.) is here correlated with age and various anthropometric parameters; the effects of exercise and of sex are considered; a chart has been constructed from which we can predict the range of P.F.R. in normal children of known height.

Material

Subjects were obtained by random selection from the records of two secondary schools and three primary schools in Inverness, a non-industrial town with approximately 30,000 inhabitants. Any child whose school medical report noted significant disease or abnormality was excluded. The sample comprises 421 children between the ages of 6 and 18 years, and is considered to constitute a representative cross-section of normal school-children in this area. Permission for testing was obtained from the parents of each child and the few refusals and absentees were replaced by children from a reserve list.

Method

Testing was carried out in the medical room of each school. Each child was weighed and the height measured, without shoes but with normal

light clothing. The surface area in each case was calculated by means of a Dubois nomogram using the directly measured height and weight readings. The object of the test was explained simply and the method of blowing the flow meter was demonstrated to the children in groups of six. Each subject then held the instrument and had several trial blows, under close supervision, until it was clear that he was using the meter properly and comfortably; this usually required two to four blows. Six successive readings of the peak flow were then recorded, excluding only the occasional faulty attempt when the subject coughed or failed to close the lips around the mouthpiece. A separate mouthpiece was used for each individual in the group. Exhortation, encouragement and small prizes were used to ensure enthusiasm, competition, maximum expiratory effort and proper recording.

Following this initial test, each child ran rapidly a distance of approximately 150 yards and, immediately on return, while still panting, recorded another six readings on the meter.

Results

Consistency of Individual Readings. From the set of six readings of peak flow rate taken from each child the average of the three maximum readings and the absolute maximum reading were compared and the difference did not exceed 5% in 96·4% of boys and 95% of girls. It was therefore considered justifiable to use the absolute maximum peak flow rate reading in each subject for the purposes of calculation and correlation.

Interrelation between Peak Flow Rate and Anthropometric Measurements. Scatter diagrams of peak flow rates in relation to height, surface area and weight are shown in Figs. 1, 2 and 3 respectively. By calculation the correlation coefficient for height and peak flow rate (r_h) = 0·930. Similarly, the correlation coefficient for surface area and peak flow rate (r_a) = 0·769. As r_a is derived from measurements of height and weight and shows inferior correlation to that of height alone, the correlation coefficient for weight need not be considered. The superiority of the correlation coefficient for height is confirmed by simple inspection of the scatter diagrams in Figs. 1, 2 and 3.

A regression or estimating equation has been employed to compare the peak flow rate firstly with height and again with surface area. In each case the sexes are considered separately and to-

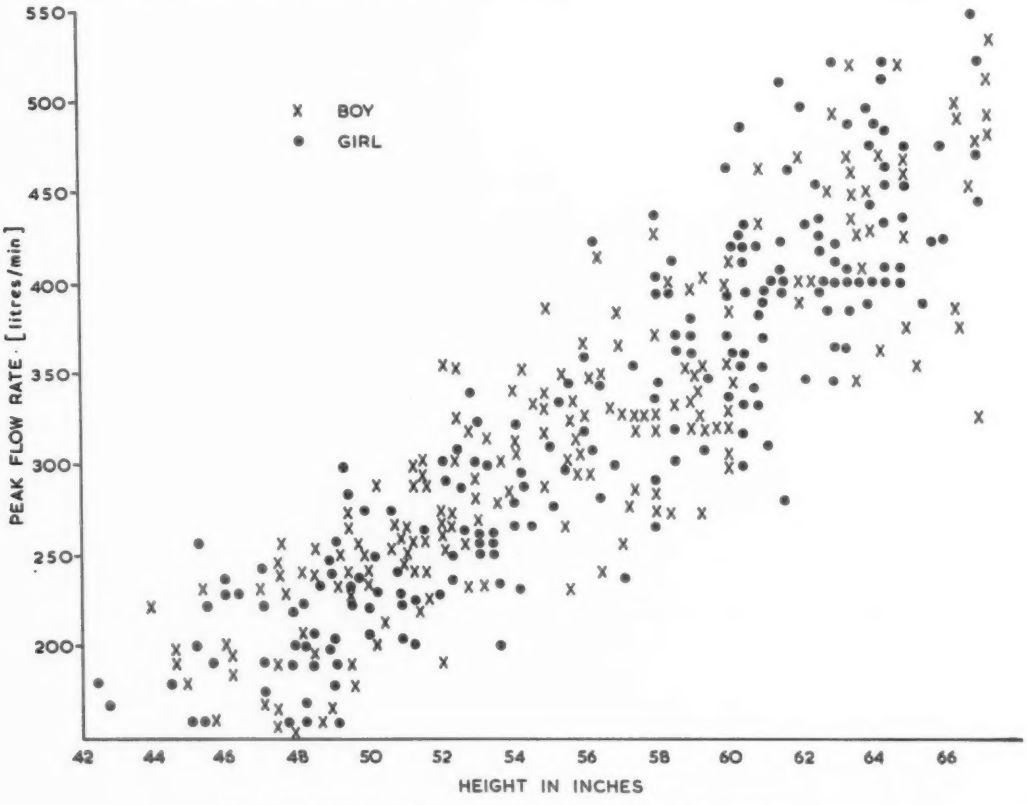

FIG. 1.—Scatter diagram showing peak flow rates in relation to height.

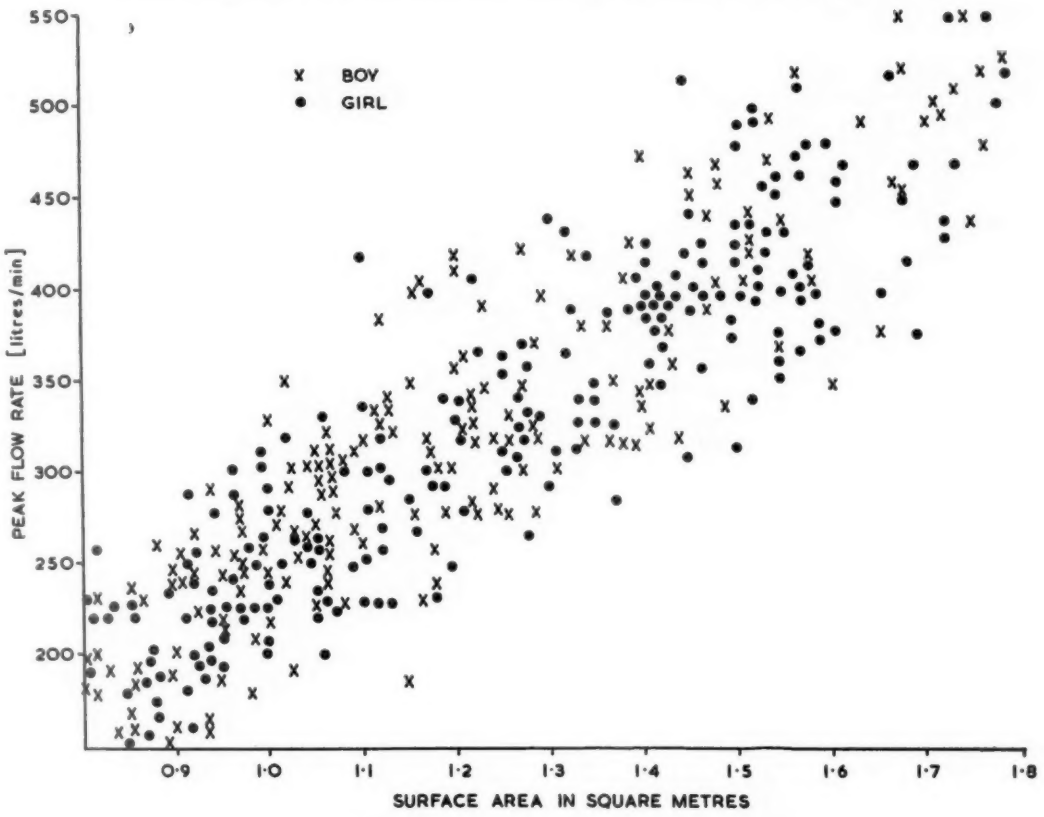

FIG. 2.—Scatter diagram showing peak flow rates in relation to surface area.

gether, giving three equations for each anthropometric measurement. The standard error of estimate which measures the scatter index is $\pm 13{\cdot}4\%$ for height and $\pm 14{\cdot}4\%$ for surface area. By means of the estimating equation and the standard error of estimate for the height values a range of normal values has been prepared in Fig. 4. This chart is based on the boys' equation. Height values were chosen in preference to surface area values as they show a lower scatter index, a higher correlation coefficient and height is easier to measure in everyday clinical work. In Fig. 4 the centre line represents the mean trend and is based on the regression equation. The scatter is depicted by the two lines on each side of the mean trend line and includes 70% of normal children within the limits of the lines marked A and 95% of normal children within the lines marked B. An estimation of the peak flow rate can be read from Fig. 4 for any desired height in children within the limits of the height of the young people investigated. The expected peak flow rate of children of known height or surface area can also be found by calculation from the regression equation $y = \mathbf{a} + \mathbf{b}x$, where y = estimated or computed peak flow rate in litres per minute, x = anthropometric measurement in inches or square metres, and **a** and **b** are constants which vary in accordance with the anthropometric measurement and whether boys, girls or adults are under consideration. The constants **a** and **b** are shown in the Table.

Sex Difference in Peak Flow Rate. Fig. 5 shows the mean trend lines based on the regression equation according to height for boys and girls. This test reveals no significant difference between the sexes.

Exercise Difference in Peak Flow Rate. Figs. 6 and 7 show the difference in peak flow rate before and after exercise of girls and boys respectively. These diagrams are based on the means of 12 height groups and not on a regression equation. A test of significance was applied to this increase in peak flow rate and it was found to be highly significant (i.e. $p = <0{\cdot}01$) in children up to 55·5 in. in height, significant (i.e. $p = <0{\cdot}05$ but $>0{\cdot}01$) in children between 55·5 in. and 61·5 in. in height, but not definitely significant in children above that height.

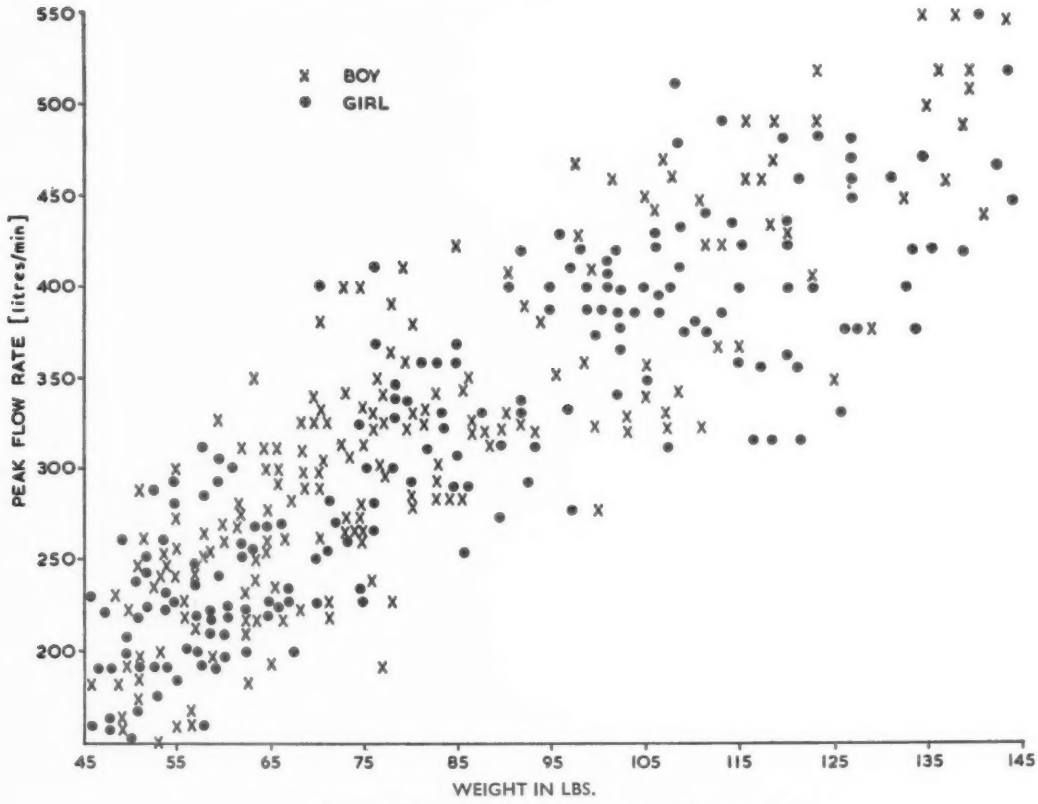

FIG. 3.—Scatter diagram showing peak flow rates in relation to weight.

Age and Peak Flow Rate. Fig. 8 shows the peak flow rate in boys and girls in age groupings. The points in the lines in the Table represent means in each group. There was a wide variation in height and weight within age groups, particularly in the boys aged 11-13 years, and this is a possible explanation for the lag in the curve at these ages.

Discussion

Using the peak flow meter in normal adults, Lockhart, Smith, Mair and Wilson (1960) found satisfactory consistency in the readings from each individual, with a variation of 6% during one period of testing compared with a variation of 11·5% in estimating F.E.V.$_{0\cdot75}$. Strang (1959) estimating

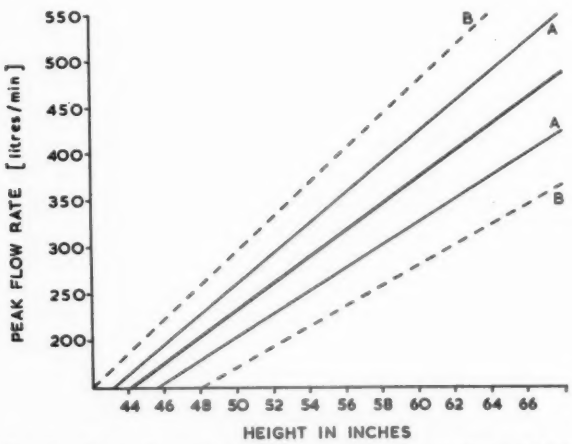

FIG. 4.—Range of normal values; peak flow rate in relation to height.

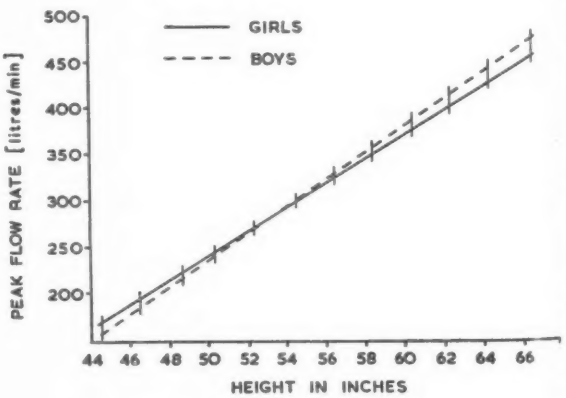

FIG. 5.—Regression lines of peak flow rates in relation to height in both sexes.

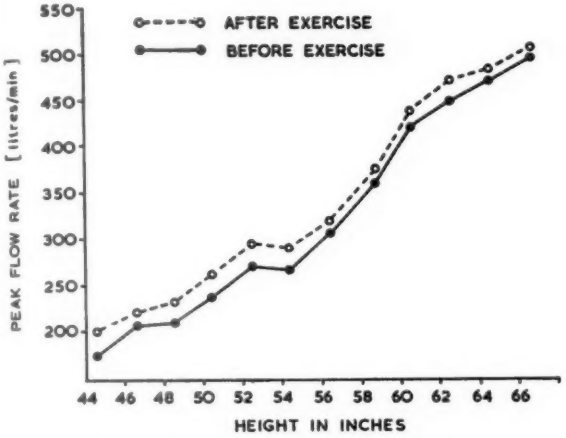

FIG. 6.—Peak flow rates in girls in relation to height before and after exercise.

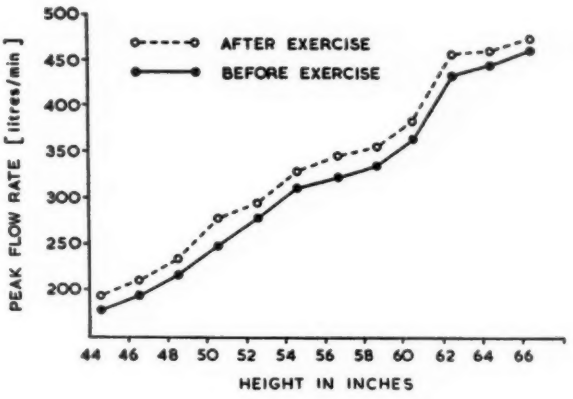

FIG. 7.—Peak flow rates in boys in relation to height before and after exercise.

FIG. 8.—Mean peak flow rate in relation to age group.

spirometrically the F.E.V.$_{1\cdot0}$ in children, based his results on the three maximum readings from each subject and found that 95% of the readings were within 3·8% of the individual means. Wright and McKerrow (1959), using the peak flow meter, also averaged each individual's three maximum results. As we are recording maximum rate of flow we feel it is more logical to base our calculations on the highest of the individual's six efforts. The concordance of our results is such that, had we used the mean of the top three, there would have been little difference in our conclusions as, in 95% of all children tested, and in 100% of those over 11 years old, these means were within 5% of the peak value.

Analysis of the results shows a positive correlation of P.F.R. with height, weight, surface area and age. The P.F.R. correlates most closely with height and surface area and much less closely with weight. There is considerable variation in height in each age group so it is not surprising that the correlation of P.F.R. with age is much less close. Even when the effect of individual variation is diminished by considering the mean P.F.R. for each age group, the resultant diagram, Fig. 8, demonstrates that the increase of P.F.R. with age is somewhat irregular and varies in the two sexes, the difference being striking after the age of 14 years and similar to that noted by Strang (1959) in his study of F.E.V.$_{1\cdot0}$. The apparent fall in P.F.R. in 11-year-old boys is possibly associated with the extreme variation of height among our subjects in this particular age group and may not be a true reflection of the population at this age. As height is the parameter which correlates most closely with the P.F.R., the relationship between these two factors is further established for each sex by the drawing of regression lines (Fig. 5) which show that, for practical purposes, the sexes may be considered together. We are thus able to draw a chart (Fig. 4) showing the mean

TABLE

	Height Groupings			Surface Area Groupings		
	Girls	Boys	Persons	Girls	Boys	Persons
a	−441·24	−476·24	−460·286	− 52·635	− 62·376	− 57·895
b	+ 13·527	+ 14·203	+ 13·893	+307·363	+323·81	+315·8

trend line for normal school-children, and the range into which fall 70% of normal children (± standard error) and 95% of normal children (± twice the standard error). Correlation of P.F.R. with the logarithm of height is even closer ($r = 0{\cdot}935$), but the difference is exceedingly small and does not, in practice, justify the extra calculation involved in what is intended to be a useful clinical index.

That the better performance of the older boys than of girls of the same age (Fig. 8) was not solely due to the boys' greater increase in height in adolescence, was demonstrated by dividing the children into four groups by height with equal weighting for the two sexes and comparing the performance of boys with girls in each group. The difference was not significant in the shortest, of moderate significance in the second group and of higher significance in the two tallest groups. It is probable that the variation between older boys and girls is associated with the onset of puberty and the different rate and manner in which the sexes reach physical maturity. No inquiry was made as to the onset of puberty in our subjects and further study will be required to clarify this point.

It has been claimed by Capel and Smart (1959) that normal adults show no change in the F.E.V. after exercise, although adults with obstructive airway disease show significant improvement. In this study, improvement in the P.F.R. occurred in every group after exercise (Figs. 6 and 7). That this improvement does not result from practice has been demonstrated by retesting a proportion of subjects after a lapse of several hours. When the effect of exercise is considered in the four height groupings already mentioned, it is found to be highly significant in the two smallest groups, of less significance in the third group, and not statistically significant in the tallest group. It is indeed apparent from the Figs. 6 and 7, and surprising to us, that the increase in P.F.R. after exercise has about the same absolute value (15 to 25 litres per minute) in all groups of children irrespective of their size. The increase is therefore relatively much larger in small children with low P.F.R.'s than in big children with big P.F.R.'s and, if the same findings continue into adult life, our results would confirm Capel and Smart's (1959) claim that normal adults, when the P.F.R. is greater still, show no significant change in F.E.V. after exercise. We can offer no explanation for this apparent effect of exercise upon the P.F.R. in normal children, but believe that it is important to take it into account when analysing the effect of therapeutic measures in obstructive airway disease.

Summary

Experience in the use of the peak flow meter of Wright and McKerrow is described.

Peak flow rates were estimated in 421 normal boys and girls and a chart was constructed from which the peak flow rate could be predicted from the child's height. The range of values found in normal children was included in this chart.

The effect of sex and exercise upon the peak flow rate in normal children was studied and the results discussed.

We wish to acknowledge our indebtedness to Dr. W. D. Wilson, Medical Officer of Health of Inverness, and his staff for a great deal of assistance in organizing our visits to the schools. We are also very grateful to Dr. J. A. MacLean, Director of Education for Inverness, and to the Headmasters and School Nurses of the schools where we studied pupils, for their assistance throughout our tests.

Dr. D. G. MacKay, Medical Statistician to the Northern Regional Hospital Board, gave generously of his time and advice in the statistical treatment of our results and we thank him for his very valuable help.

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STUDIES IN MAPLE SYRUP URINE DISEASE

BY

C. E. DENT and R. G. WESTALL
From University College Hospital and Medical School, London

(RECEIVED FOR PUBLICATION SEPTEMBER 29, 1960)

Menkes, Hurst and Craig (1954) described four infants with a progressive cerebro-degenerative disease. They were from a family of six children. Two were quite normal and of the four affected infants one survived for three months, but the others died within 14 days. An outstanding characteristic of the disease was the peculiarly pleasant smell of the urine, which was similar to that of maple syrup. Westall, Dancis and Miller (1957) reported a further clinically similar case which had survived until 20 months old. They found that the urine, which had the same characteristic odour, also contained excessive amounts of leucine, isoleucine and valine. Examination of the blood plasma revealed excessively high levels of these amino acids and also of methionine whilst the other amino acids were normal or at subnormal levels. Meanwhile, Menkes (1959) and Dancis, Levitz, Miller and Westall (1959), working on the urine from the same case, reported an elevated excretion of the branched-chain keto acids corresponding to the deaminated amino acids leucine, isoleucine and valine. Concurrently, Mackenzie and Woolf (1959), who had discovered a new case, confirmed the aminoacidaemia and aminoaciduria for the branched-chain amino acids and also independently discovered the excessive excretion of the corresponding keto acids. In 1959, the case described by Mackenzie and Woolf, which had been admitted to The Hospital for Sick Children, Great Ormond Street, under Professor A. Moncrieff, was transferred for further studies to the Metabolic Ward of University College Hospital under the care of one of us (C.E.D.).

Case Report

The earlier history of this case has been given in more detail by Mackenzie and Woolf (1959); biochemical studies are the subject of a further report in this issue (Patrick, 1961). The child, Carris O'C., was the first child of healthy unrelated parents. She was considered to be normal for the first week after birth but for the next four months made slow progress because of feeding difficulty and failure to thrive. At this stage she was noted to have occasional jerking movements of her limbs and attacks lasting a few seconds in which she became stiff and cyanosed. She showed a grossly abnormal E.E.G. Her I.Q. (Griffiths scale) was 55. Her urine showed a large excess of valine, leucine and isoleucine and of the corresponding keto acids.

On transfer to University College Hospital at the age of 8 months she weighed 7·1 kg. and measured 25½ in. in length (between 3 and 10 percentiles). There was some flexural eczema. She was grossly retarded mentally, constantly lying on her back with only occasional attempts to raise her head. She could not sit up unaided. She did not appear to be deaf, but was almost certainly blind. Her legs were usually outstretched and crossed with high tonus, her arms were usually flexed and also stiff. Limb reflexes were increased symmetrically. She frequently had attacks lasting a minute or so in which her body became stiff in opisthotonus. Feeding required perseverance and patience.

Her haemoglobin was 76%. Urine showed a slight trace of protein, but was normal on microscopy. Biochemical findings and further progress are described below. Indole chromatograms on the urine showed increased outputs of indolylacetic acid and of indolylacetyl glutamine.

Analytical Methods

The amino acid analyses of plasma and diet were carried out by the ion-exchange column chromatographic method of Moore and Stein (1954).

The method of McArdle (1957) was used for determining the keto acids in plasma and urine, but one major modification and an additional step were added which aided the identification of the higher keto acids. In the standard method the 2,4-dinitrophenylhydrazones of the keto acids which are extracted from the acidified urine or plasma by the ethanol-ethyl acetate mixture are then transferred into the aqueous phase again by extraction with 2N-NH_4OH. Whilst this is perfectly satisfactory for recovering the 2,4-dinitrophenylhydrazones of α-oxoglutaric acid and of pyruvic acid it does not give full recoveries of the less water-soluble DNP hydrazones of the keto acids with longer carbon chains which comprised the bulk of our material. Hence it was found necessary to use a more alkaline extractant. For this purpose a 1 : 1 mixture of 10% Na_2CO_3 and 2·5 N-NaOH was used. However, since there was some danger of degradation of the DNP hydrazones in this

very alkaline medium they were quickly acidified and transferred back into ethyl acetate as soon as the extraction was completed. The final volume of ethyl acetate containing the DNP hydrazones was reduced to 3 ml. (the original sample of urine or plasma was 3 ml.) and 0·5 ml. applied to the paper for chromatographic analysis. With the *n*-butanol-ethanol-0·5 N-NH_4OH (7:1:2) solvent system (McArdle, 1957) the spots due to α-oxoglutaric acid and pyruvic acid hydrazones can be cut out and measured in the usual way since they are well separated and uncontaminated by any other DNP hydrazones. However, when there is a high concentration of the keto acids of longer carbon chain length or quantities of phenolpyruvic and hydroxyphenolpyruvic acids present in the sample the DNP hydrazones of these substances all run to an area of the paper strip corresponding to a R_F value of between 0·6-0·8 and cannot be estimated separately. Therefore in assaying plasmas and urines in cases of maple syrup disease for keto acids any coloured spots with R_F values of between 0·6-0·8 were cut out and measured in the spectrophotometer and recorded as α-oxo-isocaproic acid units. In order to estimate approximately the relative composition of the mixed DNP hydrazones they were hydrogenated to yield the analogous amino acids which could then be readily identified (Towers, Thompson and Steward, 1954; Meister and Abendschein, 1956). For this purpose the remaining 2·5 ml. of the ethyl acetate extract of the mixed DNP hydrazones was taken to dryness and redissolved in 2 ml. of glacial acetic acid, 3-4 drops of 2N-HCl were added and the solution transferred to the chamber of an electrolytic desalting apparatus (Smith, 1958). During the course of 10-15 minutes the yellow colour faded leaving a water clear solution (if the yellow colour is persistent the amount of current passing is too low and a few more drops of acid are needed). The hydrogenated solution was reduced in volume (*in vacuo*) to 0·2 ml., and 0·1 ml. was applied to a large sheet of No. 4 Whatman paper for two-way separation of the amino acids (Dent, 1951), whilst the other 0·1 ml. was applied to a strip of No. 4 paper and run in water-saturated tertiary amyl alcohol with a few drops of diethylamine in the bottom of the tank (Work, 1948). The large chromatogram gave a general picture of the regenerated amino acids and the strip showed the relative concentrations of leucine and isoleucine which are not otherwise separated from each other.

Dietary Trials

Additions to Milk Diet. From the data that have accumulated so far from the studies on patients with the disease (Westall *et al.*, 1957; Menkes, 1959; Mackenzie and Woolf, 1959; Dancis, Levitz and Westall, 1960) it seems that the metabolic lesion probably occurs in the pathway of the further degradation of the keto acid derivatives of the three branched-chain amino acids leucine, isoleucine and valine. Since all three keto acids seem to be involved the metabolic block must occur early in the degradation sequence as their pathways diverge later (Coon, Robinson and Bachawat, 1955). The first step in the degradation of these keto acids is oxidative decarboxylation and condensation with a molecule of co-enzyme A (CoA). Westall *et al.* (1957) reported that their case had a high methionine and a barely detectable cystine concentration in the plasma and this imbalance of the sulphur-containing amino acids was noticed in our case also (see later). Therefore it was conceivable that the primary fault in this disease lay in an inability to convert methionine to cystine resulting in a diminished production of CoA and leading in turn to an accumulation of the branched-chain keto acids. Although, in view of the large number of reactions in which CoA takes part it seemed that such a condition would have more far-reaching effects, it was decided to carry out a trial by supplementing the patient's diet with cystine. This was later replaced by cysteine, which is more soluble and better absorbed than cystine and, moreover, does not require to be reduced before incorporation in CoA. We also tried a short course of treatment with lipoic acid, the dithiol acid which is a co-factor in the further oxidation of pyruvic and α-oxoglutaric acids, and perhaps also of the branched-chain keto acids.

On admission to this hospital the child was put on a constant milk diet with sulphafurazole 0·25 g. twice daily in continuation of therapy advised at Great Ormond Street. The first two weeks were used for control specimens of blood, urine and for E.E.G. study. The baby was then given 4 g. cystine in four divided doses of 1 g. in addition to the milk diet over a period of five days. After a six-day gap the process was repeated with 4 g. of cysteine. After a few days on the diet alone she was given 5 g. a day of sodium bicarbonate for eight days in the hope that keto acid clearance by the kidney might be increased, should their excretion be limited by processes of non-ionic diffusion as in the case of salicylic and certain other organic acids. A later opportunity was taken between dietary feeding trials to determine the possible effect of thioctic (lipoic) acid. This was given in the dose of 11 mg. a day for two days and then 22 mg. a day for two days. The plasma and urinary keto acids were measured from samples drawn on the last day of each of the separate trials and the results are presented in Table 1. Reference to this Table shows that the additional supplements to the diet had no appreciable effect on the keto acid content of the fluids examined. Moreover, semi-quantitative paper chromatographic examination of the plasma and urine for amino acids showed that the pattern was unchanged. Quantitative amino acid

TABLE 1
PLASMA AND URINARY KETO ACIDS ON MILK AND GELATINE DIETS

Diet	Plasma			Urine		
	Oxoglutaric Acid (mg./100 ml.)	Pyruvic Acid (mg./100 ml.)	Branched-chain Keto Acids (mg./100 ml.)	Oxoglutaric Acid (mg./100 ml.)	Pyruvic Acid (mg./100 ml.)	Branched-chain Keto Acids (mg./100 ml.)
Control (milk)	0·33	0·59	12·3	15·7	4·6	64·0
Control+cystine	0·40	0·65	8·7	28·0	5·6	47·0
Control+cysteine	0·32	0·91	11·7	25·0	4·0	61·0
Control+lipoic acid	0·70	1·9	9·7	4·1	2·5	42·0
Control+$NaHCO_3$	0·22	1·6	10·5	16·5	6·5	54·0
Gelatine	0·13	2·7	2·6	24·7	33·0	64·0
Gelatine+valine	0·26	1·95	2·38	11·2	11·5	55·3
Gelatine+isoleucine	0·15	2·5	2·1	24·3	13·2	68·0
Gelatine+leucine	0·07	1·0	12·4	0·4	5·2	80·5
Modified casein	0·59	2·6	2·5	12·5	27·4	16·0
Modified casein+glutamine	0·13	3·12	2·08	0·65	2·65	11·5

analyses for the control period and period on sodium bicarbonate are given in Table 3. We therefore concluded that no benefit to the baby could occur from such measures.

Restricted Intake of Leucine, Isoleucine and Valine: 'Gelatine Diet'. As the body fluids of the patient had an excessively high level of leucine, isoleucine and valine the obvious treatment was to restrict the dietary intake of these amino acids on the assumption that these high levels were harmful to the baby. The treatment of phenylketonuria was undertaken in a similar manner limiting in this case the unwanted phenylalanine by treating a protein hydrolysate with charcoal (Bickel, Gerrard and Hickmans, 1954), or by using a pure amino acid mixture in place of protein (Armstrong and Tyler, 1955). Unfortunately there is no known simple way of removing the branched-chain amino acids from protein hydrolysates. In designing a suitable diet due allowance must be made for the fact that these are essential amino acids and the dietary intake must include enough of them to allow normal growth to take place. Snyderman, Holt, Norton, Smellie and Boyer (1957) in their metabolic study on the minimum requirement of babies for valine, have given a figure of 85 mg. per kilo per day. Since figures for leucine and isoleucine were not available we have assumed here that the approximate requirement would be of the order of 115 mg. and 75 mg. per kilo per day respectively for leucine and isoleucine. A diet of this nature cannot be supplied from natural foodstuffs without lowering the total protein intake to an extremely low level. Furthermore, an entirely synthetic diet in which protein is entirely replaced by pure amino acids is costly. We therefore attempted a compromise which effected an economy without in any way reducing the total protein intake. Gelatine has comparatively lower amounts of leucine, isoleucine and valine in its amino acid composition than most other proteins. So it was decided to use gelatine in quantities (25 g. per day) which would just give the amounts of the branched-chain amino acids which were required and to use pure amino acids as supplements to bring the total amino acids up to that yielded by 40 g. of cow's milk protein. Carbohydrate and fat brought the daily calorie content up to about 1,500 per day. A mineral and a vitamin mixture were also added and

TABLE 2
THE LOW BRANCHED-CHAIN AMINO ACID DIET, BASED ON GELATINE (INTAKE/DAY)

Protein	25 g. Gelatine Yielding: (g.)	Amino Acid Supplement (g.)	Total (g.)
Alanine	2·5	—	2·5
Arginine	2·2	—	2·2
Aspartic acid	1·6	2·4	4·0
Cystine	—	7·0	9·8
Glutamic acid	2·8	7·0	9·8
Glycine	6·0	—	6·0
Histidine	0·25	1·0	1·25
Hydroxyproline	3·25	—	3·25
Isoleucine	0·40	—	0·40
Leucine	0·90	—	0·90
Lysine	1·05	1·6	2·65
Methionine	0·20	0·8 (DL 1·6)	1·0
Phenylalanine	0·60	1·9 (DL 3·8)	2·5
Proline	3·75	—	3·75
Serine	0·90	1·4 (DL 2·8)	2·3
Threonine	0·55	1·7 (DL 3·4)	2·25
Tryptophan	—	0·9 (DL 1·8)	0·9
Tyrosine	0·12	2·1	2·22
Valine	0·70	—	0·70
Total	27·97	22·0 (DL 6·7)	49·77
Fat	Arachis oil	40	
Carbohydrate	Sucrose	70	

Mineral mixture: Calcium lactate 8·0 g., calcium chloride ($CaCl_2$, $2H_2O$) 0·5 g., dipotassium hydrogen phosphate 3·0 g., disodium hydrogen phosphate 1·88 g., magnesium sulphate 1·25 g., ferrous sulphate 6 mg., copper sulphate 5 mg., zinc chloride 5 mg., potassium iodide 0·25 mg., potash alum 1 mg., cobalt sulphate 1·0 mg., sodium molybdate 0·7 mg.

Vitamin mixture: Vitamin A 5,000 i.u., vitamin D 1,000 i.u., aneurine 1·0 mg., riboflavin 0·4 mg., pyridoxine 0·5 mg., nicotinamide 5 mg., ascorbic acid 25 mg., folic acid 0·5 mg., choline chloride 75 mg., *p*-aminobenzoic acid 1·0 mg., biotin 50 µg., vitamin B_{12} 10 µg.

the whole diet was designed to simulate an intake equivalent to that of a litre of milk each day. The composition of the diet is given in Table 2.

The patient was maintained on this diet for 35 days. On the seventh and fourteenth days blood and urine samples were collected for analysis. The keto acids were determined, the amino acids were examined by paper chromatography and a quantitative determination of the plasma amino acids was carried out by the Moore and Stein (1954) ion-exchange resin column method. From now on we attempted to determine whether the baby could metabolize individual branched-chain amino acid when added separately to the diet. From the fifteenth to the nineteenth day the basic diet was supplemented with an additional 1·8 g. of valine per day (to raise the total valine to the amount in 40 g. of milk protein). On the 20th to the 22nd day the diet was given unaltered in order that equilibrium might be attained before adding a supplement of isoleucine (2 g. per day) each day for five days. After re-equilibration on the basic gelatin diet, 3·6 g. of leucine was added each day for a further five days. The analytical results are given in Tables 1 and 3.

There were no apparent clinical signs of improvement in the condition of the patient during the period on the dietary trial, but she continued to gain weight. There was some vomiting during the time when the leucine level was raised. The plasma amino acid concentrations approached normal levels during periods without supplementation by the branched-chain amino acids and the plasma concentration of the branched-chain keto acids fell from 10-12 to about 2 mg./100 ml. However, a most striking feature was the disappearance of the characteristic smell from the urine. The replacement of a normal level of valine to the diet raised the plasma level for that amino acid to 46 mg./100 ml., but did not alter significantly the keto acid level. Similarly, the addition of isoleucine raised the plasma level of this amino acid to 27·6 mg./100 ml., but again the total branched-chain keto acid level in the plasma was unchanged. By contrast, when the leucine was added to the diet the plasma level of leucine rose to 36·7 mg./100 ml. as expected, but also the branched-chain keto acids increased to 12·4 mg./100 ml., and this figure was largely due to α-oxoisocaproic acid, the keto acid of leucine. Moreover, the maple syrup odour returned to the urine.

When the patient was put on the gelatin diet some more subtle changes in the plasma amino acid levels occurred, some of which were difficult to interpret. For some reason the levels of serine and threonine were high, up to four times normal, during the first three weeks, but dropped to normal levels later. Also the asparagine + glutamine concentration was low at the beginning, but increased later. The respective levels of methionine and cystine approached normal on the partially synthetic diet, but it was difficult to see why the methionine level should rise to 9 mg./100 ml. when the isoleucine intake was returned to normal.

With respect to the urinary excretion of amino acids on the gelatin diet, leucine, isoleucine and valine were constantly seen on the paper chromatograms, although the amounts were less than when the patient was on the milk diet. This, presumably, is a reflection on the blood levels of these amino

TABLE 3

PLASMA AMINO ACIDS ON MILK AND GELATINE DIETS

Amino Acid	Control (Milk Diet) (mg./100 ml.)	Control +$NaHCO_3$ (mg./100 ml.)	Gelatine Diet (mg./100 ml.)	Gelatine Diet + Added Valine (mg./100 ml.)	Gelatine Diet + Added Isoleucine (mg./100 ml.)	Gelatine Diet + Added Leucine (mg./100 ml.)
Alanine	1·47	(3·3)*	2·87	(5·19)*	3·17	1·13
Arginine	—†	1·30	—	1·16	2·03	1·42
Asparagine+glutamine	1·96	4·80	2·00	2·32	8·66	6·18
Aspartic acid	0·14	0·14	0·74	0·24	0·22	0·35
Cystine	0·0	0·0	1·17	0·92	0·56	1·11
Glutamic acid	0·50	—	1·77	0·97	—	—
Glycine	0·90	(3·3)*	5·82	(5·19)*	4·91	4·00
Histidine	0·80	1·19	—	1·34	1·21	1·45
Isoleucine	8·50	8·30	1·87	1·85	27·6	0·50
Leucine	21·1	25·0	5·68	4·60	4·45	36·7
Lysine	0·7	1·53	—	1·61	2·57	1·36
Methionine	3·90	3·22	0·98	1·67	8·99	1·70
Ornithine	—	—	—	1·28	1·13	0·95
Phenylalanine	0·90	1·42	3·50	2·07	3·50	4·45
Proline	—	1·60	3·25	—	—	—
Serine	1·20	1·55	6·89	3·85	3·42	1·68
Taurine	—	0·70	1·64	1·96	1·90	2·20
Threonine	0·90	2·57	6·41	4·40	1·09	1·19
Tyrosine	0·80	1·45	3·07	1·90	2·51	1·90
Valine	14·5	15·5	6·46	42·6	7·30	2·99

* Glycine + alanine.

† The dashes indicate that no analysis was obtained for technical reasons.

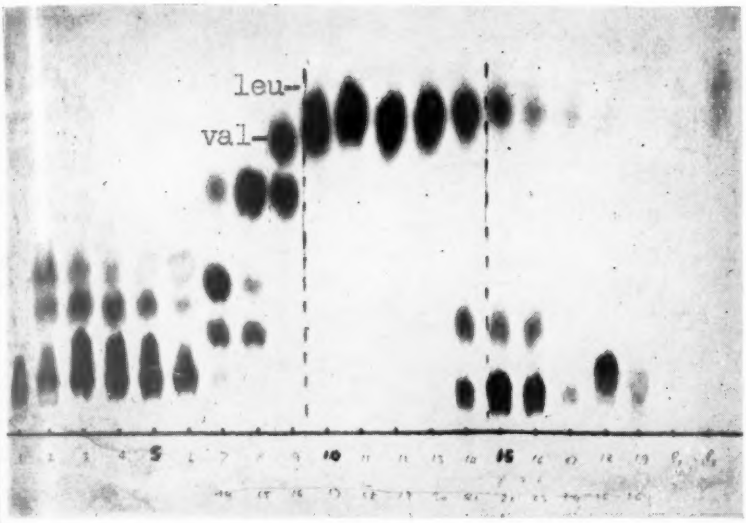


FIG. 1.—Paper chromatographic analysis of the amino acids present in the fractions obtained from the ion-exchange resin column. The acidic amino acids are found in the early fractions, followed by the neutrals, whilst the basic amino acids occur in the later fractions.

acids which, although much reduced on this diet, were still above normal. It appears that the dietary intake of these amino acids could be further reduced with benefit to the baby. The urinary excretion of keto acids was always high, but it was largely artefactual since the total figure was raised by the presence of large amounts of phenylpyruvic acid derived from *d*-phenylalanine as this amino acid was added to the diet in the racemic form.

After these trials were over the cost of the diet forced us to return her to a milk diet again. The results of the trial seemed to point to leucine being the major amino acid implicated in the disturbance of metabolism. It contributed to most of the keto acid production and to the urinary odour. Clinically she was not so well when this amino acid was replaced in the diet in normal quantities; she vomited on several occasions and she was more restless. However, she was also unable to metabolize the valine and isoleucine when they were given separately.

Modified Casein Hydrolysate Very Low in Leucine. It has already been pointed out that it is impossible to provide a natural diet adequate in terms of total protein which will supply at the same time the much-reduced quantity of the branched-chain amino acids which appear necessary for the well-being of this patient. However, such a diet can be prepared in the laboratory at no great cost in raw materials, but with a considerable expenditure of time and labour. Casein was hydrolysed with strong acid and the liberated amino acids fractionated by means of charcoal extraction and passage through a column of a cationic exchange resin, following the procedure described by Partridge (1949) except that the ion-exchange resin Zeo-Karb 225 was used instead of Zeo-Karb 215. The apparatus and the procedure have been briefly described in an article on ion exchange resins (Westall, 1961). The fractions obtained were analysed for amino acids by paper chromatography and the results are illustrated in Fig. 1. It will be seen that by rejecting fractions 10-14 inclusive most of the leucine and isoleucine and about one half of the valine can be excluded. Thus by recombining the remaining fractions, adding back the phenylalanine and tyrosine, which were recovered from the charcoal residue, and compensating for the losses of cystine, methionine, histidine, lysine and tryptophan, an amino acid mixture was obtained which had much-reduced levels of the branched-chain amino acids. The analysis of the mixture in terms of the amounts of the various amino acids present in the diet each day is given in Table 4. The other non-protein components of the diet were the same as for the previous trial, the new amino acid mixture replacing the gelatine + amino acid supplements used before. The total weight of amino acids (24 g.) given each day during the new trial was lower than we would have wished, but by giving this amount we were just able to match the rate of laboratory production of the mixture with the rate of consumption by the patient. This was kept up for a period of six weeks. With the new amino acid mixture the leucine, isoleucine and valine intake was 0·2, 0·3 and 1·8 g. respectively.

The patient took the diet well and continued to grow satisfactorily throughout the trial period. Again the maple syrup smell of the urine which had quickly returned whilst on the milk diet, disappeared. The plasma level of the branched-chain keto acids fell to 1·1 mg. per 100 ml. (Table 1), the lowest concentration achieved so far. However, the concentration of isoleucine in the plasma was 9·9 mg. per 100 ml. in spite of the low intake of this amino acid and we were astonished to find that the plasma valine level had risen to 76·5 mg./100 ml., although the valine content of the diet was only about two-thirds of that in the milk diet. The methionine level was also well above normal, but the cystine, although low, was just within normal limits. The plasma level of glutamine appeared

TABLE 4
PLASMA AND CEREBROSPINAL FLUID AMINO ACIDS ON MODIFIED CASEIN HYDROLYSATE DIET

Amino Acid	Diet Intake (g./24 hrs)	Plasma		C.S.F.	
		Diet Only (mg./100 ml.)	Diet+Glutamine (mg./100 ml.)	Diet Only (mg./100 ml.)	Diet+Glutamine (mg./100 ml.)
Alanine	1·00	1·90	1·70	0·21	0·46
Arginine	0·50	1·40	—	—	—
Asparagine+glutamine	—*	1·80	2·10	1·40	2·81
Aspartic acid	2·10	0·22	0·00	0·07	0·00
Cystine	0·80	0·70	0·50	0·00	0·00
Glutamic acid	5·50	1·00	0·50	0·00	0·00
Glycine	0·60	3·00	3·00	0·43	0·48
Histidine	1·10	1·50	—	0·78	—
Isoleucine	0·30	9·90	7·50	0·73	0·60
Leucine	0·20	1·10	0·32	1·28	1·14
Lysine	1·40	1·77	2·50	0·51	—
Methionine	1·40	3·90	5·50	0·02	—
Ornithine	—	0·90	0·86	0·22	—
Phenylalanine	0·50	0·60	0·64	0·24	—
Proline	2·40	—	—	—	—
Serine	1·50	2·60	1·40	0·64	0·56
Taurine	—	1·00	0·77	0·91	0·95
Threonine	1·20	4·90	2·50	0·94	0·52
Tyrosine	0·90	1·10	1·60	0·31	—
Valine	1·80	76·5	77·8	11·8	9·8

* The dashes indicate that no analysis was obtained for technical reasons.

to be low, but the recovery of this amino acid is well known to be variable when estimated by the Moore and Stein method. However, in view of this, during the latter part of the trial with the modified casein hydrolysate the daily diet was supplemented by the addition of 5 g. of l-glutamine. Analysis of the plasma sample taken after five days showed only a slight rise in the glutamine level and confirmed the high valine figure. The plasma leucine level had fallen further to 0·32 mg. per 100 ml., which indicated that if a further trial was carried out the leucine intake should be slightly raised.

Studies on the Cerebrospinal Fluid. We were especially interested to consider changes in the composition of the baby's C.S.F. in case these might mirror the clinical changes more accurately than would analyses of blood. The paper chromatographic pattern of the amino acids of 625 µl. of normal deproteinized C.S.F. shows a strong spot due to glutamine and much weaker spots of alanine, glycine, serine and barely discernible spots due to valine, leucine(s), tyrosine and lysine (Dent and Walshe, 1954). In fact, apart from the glutamine, it reflects a weakened version of the blood plasma picture. When the patient was on the milk diet her C.S.F. amino acids were found to be mimicking the situation in the blood with abnormally high concentrations of leucine, isoleucine and valine, higher in fact than the concentration of glutamine. These levels were reduced later with respect to leucine and isoleucine when the patient was on the modified casein-hydrolysate diet, but the valine level remained high.

In the same way the branched-chain keto acids in the C.S.F. reflected the concentration of these amino acids in the blood plasma. When the plasma contained 11 mg. per 100 ml. of the total branched-chain keto acids the C.S.F. level was 3·1 mg. per 100 ml. and when the plasma level dropped to 2·1 mg. per 100 ml. on the modified diet the C.S.F. concentration also dropped to 0·85 mg. per 100 ml. Further, at the higher level of 3·1 mg. per 100 ml. of total branched-chain keto acids in the C.S.F. the keto derivatives of leucine, isoleucine and valine were represented. But later, when on the modified diet, valine was the only amino acid which was excessively high in the plasma. This led to a high level of α-oxoisovaleric acid also in the plasma and once again the value of 0·86 mg. per 100 ml. of total branched-chain keto acid in the C.S.F. was almost entirely composed of α-oxoisovaleric acid (Table 5).

TABLE 5
CEREBROSPINAL FLUID KETO ACIDS

Diet	α-oxoglutaric Acid (mg./100 ml.)	Pyruvic Acid (mg./100 ml.)	Branched-chain Keto Acids (mg./100 ml.)
Control—milk diet	0·33	1·34	3·15*
Modified casein diet	0·04	1·20	0·85†
Modified casein + glutamine	0·06	0·71	0·86†

* Mainly α-oxoisocaproic acid.
† Mainly α-oxoisovaleric acid.

On the modified diet, with and without added glutamine, the values for α-oxoglutaric acid and pyruvic acid in the C.S.F. were well within normal limits, but the α-oxoglutaric acid level of 0·33 mg.

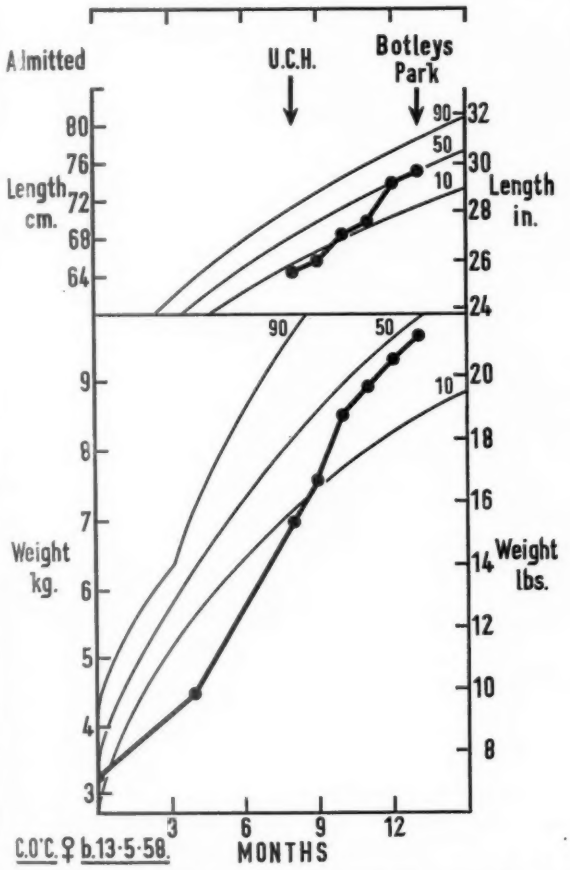


FIG. 2.—Growth data for C.O'C. The growth while on our various diets at U.C.H. can be noted.
The normal percentiles are copied from the charts prepared by Dr. H. C. Stuart (Children's Medical Center, Boston, Mass.).

per 100 ml. was found when the patient was on the milk diet. This matched the concentration in the plasma measured at the same time. On the evidence of a single determination we cannot say whether this is significant or not.

Further Clinical Data. It has been mentioned above that the baby's general condition remained practically unchanged during the dietary trials, with only a suspicion that she worsened when given a disproportionate amount of leucine. The growth curves (Fig. 2) show that as far as general nutrition was concerned she did well, passing from the 3 percentile to the 50 during the whole period on the various diets, during which her biochemistry became intermittently normal according to the particular trial in question. An unexpected finding on the modified casein hydrolysate diet was that a few days after beginning it all the baby's hair came out and showed no evidence of regrowth while in hospital subsequently. We were especially interested to perform E.E.G.s at various stages in the treatment as there seemed a possibility that these might change more quickly than the child's observed behaviour. One was done while on the milk diet, one after 13 days on the gelatine diet while the baby's biochemistry was practically normal, and one after each period of loading with valine, leucine and isoleucine. All were grossly abnormal and showed no definite differences under the various dietary conditions.

While on the milk diet, soon after admission, timed blood and urine collections were obtained for amino acid clearance determinations. These showed low normal clearances for all the amino acids; in particular the clearances for valine, leucine and isoleucine were 0·1, 0·1, 0·1 ml. per min. respectively, all below the normal range. This confirmed the 'overflow' mechanism for the aminoaciduria and excluded renal factors whether primary or secondary to the amino acid or keto excretions.

Of interest was the fact that during periods of relatively normal biochemistry the excretion of indolic acids in the urine became normal. Clearly this abnormality must in some way be an induced artefact as is the case with the almost identical abnormality found in phenylketonuria.

On June 20, 1959, the baby was transferred to Botley's Park Hospital pending the arrival from the United States of America of a large quantity of pure amino acids kindly offered to us for her further dietary treatment. She had, meanwhile, been put back on her previous milk diet. She did not do too well on this and unfortunately died on August 23, 1959, a few days before the arrival of the supply of the amino acids. A detailed autopsy was carried out and will be published elsewhere (Crome, Dutton and Ross, 1961).

Discussion

One of us (R.G.W.) had the opportunity of working on a previous baby with this disease (Dancis *et al.*, 1960) and one of the striking features of the present study has been the close similarity in the grossly abnormal plasma and urine amino and keto acid patterns in the two cases. The identical patterns have also been noted in the urine of a further case, kindly sent to us by Dr. D. Gairdner. As the diagnostic amino acid patterns have not yet been published we illustrate these in Figs 3a and b. We agree with the earlier workers that there is an accumulation in the plasma of the keto acids α-oxoisocaproic, α-oxomethylvaleric, α-oxoisovaleric acids and possibly also of α-oxomethiolbutyric acid, but further stress that of these the

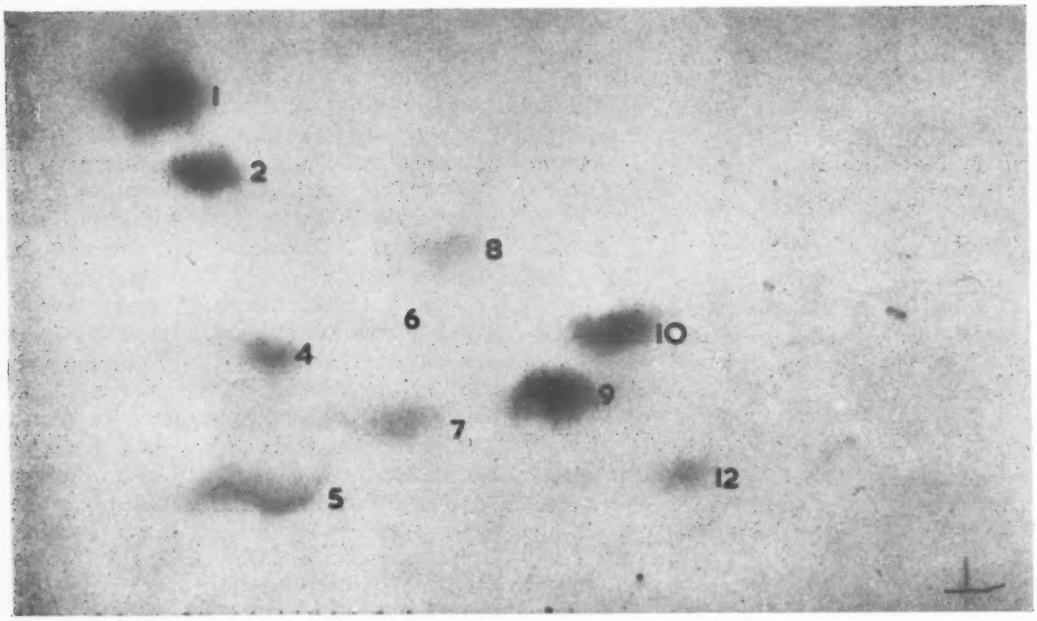


FIG. 3a.—A paper chromatogram of the urine of patient C.O'C. The volume of urine applied to the paper was 45 µl. and contained 0·25 mg. of total N.

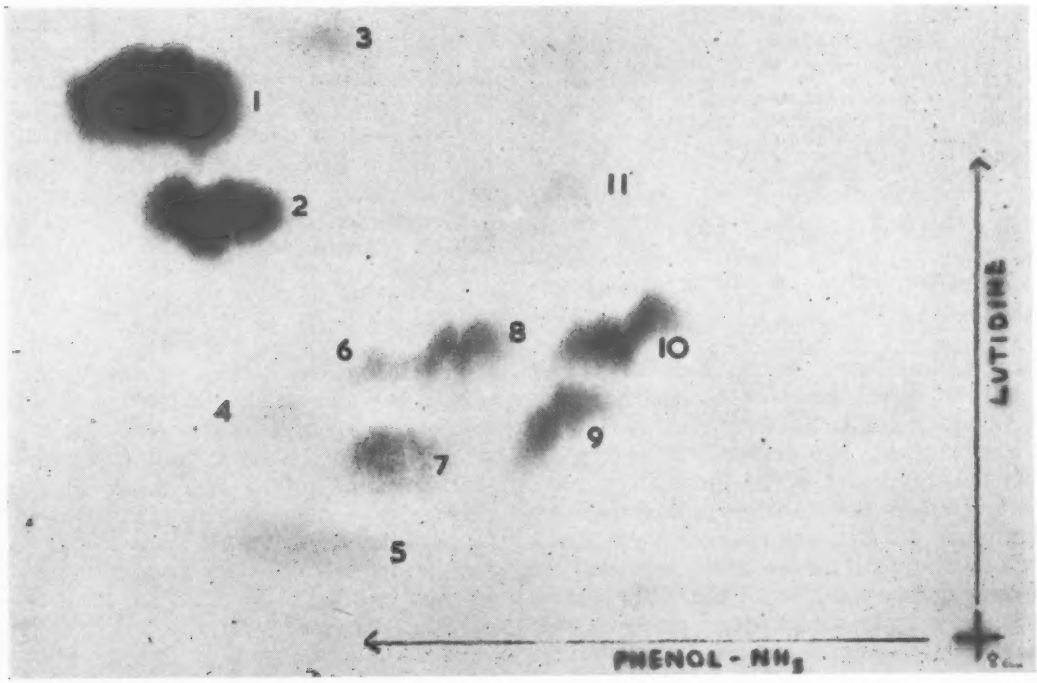
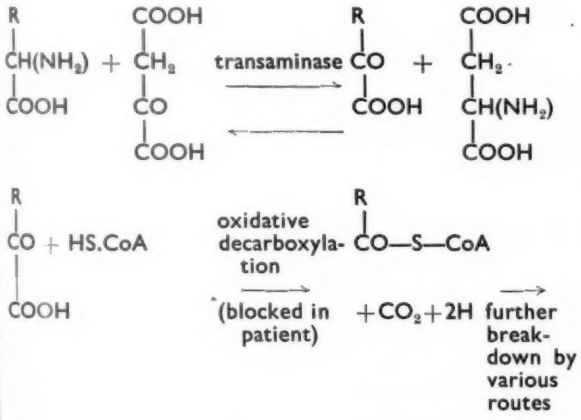


FIG. 3b.—A paper chromatogram of the plasma of patient C.O'C. 625 µl. of deproteinized and desalted plasma was applied to the paper. 1, leucine and isoleucine; 2, valine; 3, tyrosine; 4, histidine; 5, lysine; 6, alanine; 7, glutamine; 8, threonine; 9, glycine; 10, serine; 11, taurine; 12, glutamic acid.

predominant constituent by far is α-oxoisocaproic acid. This is the keto acid derived from leucine. We have also shown from our dietary experiments that the metabolite in the urine responsible for its characteristic smell is also derived from leucine. This made us wonder for a time if leucine was the key amino acid whose metabolism was primarily disturbed, the other amino acids being affected by some secondary mechanism such as substrate competition. It was tempting to try and relate the whole disorder to one metabolic block due to an inborn deficiency of one enzyme. We had this in mind when we designed our feeding trial with the modified casein hydrolysate. This was made very low in leucine, less low in isoleucine and only slightly low in valine. The results, when they came through, of the earlier trial on the gelatin diet taken together with those giving modified casein hydrolysate clearly indicated that each of the three branch amino acids demonstrated a gross metabolic block independently of the others. Hence, if we wish to support the classical genetic theory of one gene one enzyme, we are forced to suggest that the three amino acids share a common metabolic pathway and that this is at the stage of oxidative decarboxylation of their keto acid derivatives as shown below, where R represents the carbon chain of the amino acid in question.



Our results, therefore, support the suggestions already made by Dancis *et al.* (1959), Mackenzie and Woolf (1959) and Menkes (1959).

The suggestion above does not preclude the possibility of secondary metabolic blocks consequent on the grossly abnormal plasma levels of metabolites in the untreated state. It is of note here that on the control milk diet the plasma levels of each branched-chain amino acid were lower than on the experimental diets to which the particular amino acid was added in the same amount as on the milk diet. The valine level, for instance, was about 15 mg. per 100 ml. on the milk diet but rose to 42·6 when valine was added to the gelatin diet (Table 3) and to about 77 on the slightly lower intake on modified casein hydrolysate (Table 4). This suggests that the body coped even worse with the one amino acid in turn when the amino acid imbalance was exaggerated in this way. Some information is, in fact, available which shows the effect of inducing this type of amino acid imbalance. Snyderman, Cusworth, Roitman and Holt (1959) showed that the omission of leucine from an otherwise normal diet fed to two normal infants reduced the plasma leucine level as expected, but also caused a marked rise in the plasma valine concentration. Likewise, in our experiments the high methionine levels on the milk diet (with low cystine) could well have been due to competition with methionine of the branched amino acids since this was largely corrected on the gelatin diet. This possibly induced metabolic block seemed more sensitive to isoleucine than to the other branched-chain amino acids since on the gelatin diet the methionine level in the plasma only rose when isoleucine was added, not with valine or leucine. Other probable induced metabolic blocks in the untreated state are indicated by the high indolic acid excretion, recalling that occurring in untreated phenylketonuria.

With regard to the feeding trials which we carried out, we now have reason to believe that it should be possible with similar forms of diet to adjust quite accurately the amino acid intake of the branched-chain amino acids of methionine so as to allow enough for growth while still maintaining normal plasma amino and keto acid levels. Unfortunately this is a costly procedure at present, but now that the disease has been recognized and is easy to detect, it may well prove to be less rare than we think. This would certainly justify pilot-scale production of a suitable amino acid mixture obtained from casein hydrolysate in the manner indicated here.

We are still left wondering how far the patient's whole clinical picture might have been immediately related to the gross metabolic abnormality found. There seemed to be no detectable improvement in her neurological state whilst her biochemistry was made more or less normal by means of the modified diets. This could well have been because the damage already done to the central nervous system was irreversible, as it is also believed to be in cases of phenylketonuria which are treated after 1 year of age. It was encouraging to note that during the various dietary trials the patient continued to grow at a steady rate and her physical condition

was satisfactory. There was certainly no progression of the disease so we are left in the hope that a diet designed to avoid the excess of amino and keto acids might be instrumental in preventing the damage. From the cases so far described (Menkes *et al.*, 1954) and two other cases which have recently come to our notice (Gairdner, unpublished) the disease may have a fatal outcome within 14 days so that an early diagnosis is particularly essential. Apparently the first clinical sign is seen at about 4-5 days of age when the child shows a reluctance to feed. The maple syrup odour may develop some days later and may easily be overlooked unless it is looked for particularly.

Summary

Further studies have been undertaken of a baby with maple syrup urine disease.

Of the various methods tried only diets low in the branched-chain amino acids were able to make normal the observed metabolic abnormalities.

No clinical improvement was noted during our dietary experiments. They were, however, of short duration and were probably applied too late.

The metabolism of the three keto acids derived from leucine, isoleucine and valine seemed to be grossly impaired presumably because they shared a common pathway at one point.

A method is described of preparing a casein hydrolysate low in leucine, isoleucine and valine and potentially capable of adaptation to larger scale production.

The authors acknowledge with gratitude a grant from the Nuffield Foundation, through the courtesy of Professor L. S. Penrose, which enabled them to purchase the amino acids used in the dietary trials. They also thank Miss E. Davies, who carried out the Moore and Stein analyses, and the dietitian (Mrs. B. Hartland), Sister (Miss M. Wilmot) and nurses of the Metabolic Ward, University College Hospital, London.

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MAPLE SYRUP URINE DISEASE

BY

A. D. PATRICK

From the Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London

(RECEIVED FOR PUBLICATION AUGUST 3, 1960)

A familial syndrome characterized by gross mental retardation, a urine odour resembling maple syrup, and a short fatal course, was first described by Menkes, Hurst and Craig (1954). Two similar cases have since been reported (Westall, Dancis and Miller, 1957; Dancis, Levitz, Miller and Westall, 1959; Mackenzie and Woolf, 1959), in which markedly raised levels of leucine, isoleucine and valine were found in urine and plasma. Analysis also revealed high concentrations of the α-keto acids derived from these branched-chain amino acids by transamination (Menkes, 1959).

These abnormalities could result from a defect in the further degradation of the keto acids, for which the most probable normal pathway involves a common mechanism of oxidative decarboxylation (Coon, Robinson and Bachhawat, 1955; Fig. 1), and recent work has sought to substantiate this inference.

A study of one of the cases mentioned above has been summarized recently by Dancis, Levitz and Westall (1960). The further biochemical investigation of the other case was undertaken at this hospital, and the results obtained are presented in this report.

Case History

A full report on first admission of the child to The Hospital for Sick Children has been given by Mackenzie and Woolf (1959). Dietary trials carried out at University College Hospital are the subject of the previous paper in this issue (Dent and Westall, 1961).

The patient, a girl, was the only child of healthy, unrelated parents, with no family history of mental deficiency. She appeared normal at birth, but stopped sucking at 1 week, and had to be fed by tube.

On admission to The Hospital for Sick Children, aged 4 months, she was severely mentally retarded, and some jerking of the limbs was noted. The urine possessed a persistent odour resembling burnt sugar, and analyses of urine and plasma for amino and keto acids confirmed the suspected diagnosis of maple syrup urine disease. A diet containing glycine as the sole amino acid was tried, but no improvement in the clinical or biochemical findings was observed. When 8 months old she was transferred to the metabolic unit of University College Hospital, for further investigation of restricted diets, and from there was admitted to Botley's Park Hospital, where she died on August 23, 1959, aged 15 months. The post-mortem findings are to be published by Crome, Dutton and Ross (1961).

Materials and Methods

A 24-hour collection of urine from the patient at 8 months of age had been stored at −25° C. for nine months. Post-mortem specimens of liver, kidney and brain were frozen immediately and kept at −25° C. Control specimens from a patient of about the same age, who died from congenital heart disease, were treated in the same manner.

Chromatography. Amino acid chromatography was carried out in the usual way on Whatman No. 1 paper, using n-butanol-acetic acid-water (12:3:5 by vol.) as solvent system. Tissue incubation media were deproteinized with ethanol, and concentrated to small volume for analysis. These solutions were analysed also for metabolic intermediary acids (Lugg and Overell, 1948). For the detection of coenzyme A derivatives (Stadtman, 1952), media were deproteinized by an equal volume of ethanol adjusted to *p*H 4·5 with 0·1 N sodium acetate buffer.

Urinary keto acids were characterized as the 2:4-dinitrophenylhydrazones in a butanol-ethanol-ammonia solvent (El Hawary and Thompson, 1953). Trichloracetic acid filtrates of tissue media were analysed similarly. The α-ketoisocaproic acid used as a standard was obtained from the California Corporation for Biochemical Research, Los Angeles, and purified by recrystallization of the barium salt from aqueous acetone.

An ether-soluble fraction of acidified urine was obtained by continuous extraction for 12 hours. After removal of ether, the residual oil was dissolved in dilute ammonia, and chromatographed on Whatman No. 2 paper, with a solvent system, n-butanol-n-propanol-0·1 N ammonia (2:1:1 by vol.). Ammonium salts produced red spots when sprayed with diazotized p-nitroaniline and alkali (Whitfield, 1960). Further information on the identity of the spots was obtained by using 2:4-dinitrophenylhydrazine and ferric chloride-phenol as spray reagents.

Identification of α-Hydroxy Acids. Some conversion of urinary α-hydroxy acids to the corresponding keto

acids was obtained by careful oxidation with Fenton's reagent. Urine (2 ml.) was diluted to 5 ml. with water, and cooled to 0° C. Ferrous sulphate solution (0·1 ml. of 0·001 M) and hydrogen peroxide (0·1 ml. of 0·2%) were added, and the mixture kept at 0° C. for six hours. While still cold, 0·4 ml. of a saturated solution of 2:4-dinitrophenylhydrazine in 2N HCl was added, and the mixture allowed to warm to room temperature. Extraction and chromatography of the resulting hydrazones was carried out as before.

Areas of paper occupied by individual spots were cut from a preparative chromatogram, and disintegrated in dilute acetic acid. The amino acids derived from these hydrazones by electrolytic reduction (Smith, 1958) were then identified by chromatography.

Tissue Experiments. Tissue homogenates were prepared in the appropriate ice-cold solutions, using an all-glass homogenizer of the Potter type.

Transamination. Incubation mixtures contained L-leucine (0·01 M), pyruvate or α-ketoglutarate as the sodium salts (0·01 M), and 4 ml. of a 10% tissue homogenate in 0·1 M phosphate buffer, *p*H 7·4, in a total volume of 10 ml. The tests were run anaerobically at 37° C. Transamination was followed by periodic analysis for amino and keto acids.

Oxidative Decarboxylation. Tests for the anaerobic production of carbon dioxide were carried out by the standard Warburg method, using a medium of the following composition (concentrations expressed in μmoles): potassium phosphate, *p*H 7·4, 200; magnesium sulphate, 2·5; cysteine, 10; diphosphopyridine nucleotide (DPN), 0·2; keto acid, K salt, 50; coenzyme A, 10; thiamine diphosphate, 0·2; adenosine diphosphate (ADP), 10. Tissue slices, or a 10% homogenate in 0·05 M phosphate, *p*H 7·4 (1 ml.), were used in a final volume of 2 ml. Incubation temperature was 37° C.

Results

The characteristically raised levels of leucine, isoleucine and valine, and of the corresponding keto acids were the most prominent features of urine analysis. The 24-hour excretions of leucine and α-ketoisocaproate were approximately 25 mg. and 65 mg., respectively. The keto acid pattern also showed an abnormally high level of α-ketoglutarate.

The presence of α-hydroxy acids in the urine was indicated by comparison of its reaction with 2:4-dinitrophenylhydrazine before and after oxidation with Fenton's reagent. The reaction was greatly increased after oxidation, the component showing greatest change (R_F 0·82) coinciding with the dinitrophenylhydrazone of α-ketoisocaproic acid. This identity, and the presence of the superimposed hydrazone of α-keto-β-methylvaleric acid, was confirmed by the formation of increased amounts of leucine and isoleucine by electrolytic reduction. From these results it may be concluded that the urine contained α-hydroxy-isocaproic and α-hydroxy-β-methylvaleric acids, the derivatives of leucine and isoleucine, respectively. The acid corresponding to valine, namely, α-hydroxy-isovaleric acid, could not be detected by these methods.

Further confirmation of the identity of the urinary acids was derived from chromatography of the ether extractives. Two main components were coloured red by the diazo reagent, and each could be further resolved into two by the use of alternative spray reagents. The faster-moving areas (R_F 0·50 and 0·38) reacted strongly with dinitrophenylhydrazine, and coincided with α-ketoisocaproic and α-ketoisovaleric acids, respectively. The slower-moving areas (R_F 0·46 and 0·35) reacted for α-hydroxy acids in giving a yellow colour with a phenol-ferric chloride spray, and coincided with α-hydroxy-isocaproic and α-hydroxy-isovaleric acids, respectively.

The oil derived from the ether extract also possessed much of the maple syrup odour, and this was found to be concentrated in two spots (R_F 0·56 and 0·42) on the chromatograms. These constituents were completely separated from the above-mentioned acids, and were stained yellow by the diazo reagent, thereby differing from carboxylic compounds. Immediate reaction also occurred with dinitrophenylhydrazine and with ammoniacal silver nitrate. Some separation of the 'maple syrup substances' was obtained by gently warming the oil, to which a few drops of water had been added. Colourless needle crystals were deposited rapidly in the neck of the flask, and were shown to contain the 'maple syrup substance' of R_F 0·56, together with some α-hydroxy-isovaleric acid, by chromatography of a solution in dilute ammonia. The crystals were extremely volatile, disappearing in a few minutes on exposure to the air at room temperature.

Enzyme Experiments. The rates of transamination in a leucine-pyruvate system, as measured by the formation of α-ketoisocaproate, were approximately the same for tissues of the experimental and control cases. It was observed also that pyruvate gave rise to α-ketoglutarate when these test media were incubated aerobically. While its initial rate of formation in the maple syrup urine case was much slower than that of the control the eventual concentration attained was considerably higher. This suggested further utilization in the control tissues, and this conclusion was borne out by the progressive appearance of succinate. No succinate was formed by tissues of the maple syrup urine case.

Oxidative decarboxylation of α-ketoisocaproate could not be detected in homogenates or slices of the experimental and control tissues. In a further control case, from which liver had been stored frozen for only one day, low activity was detected in homogenates. After storage for one week this activity had disappeared entirely. Using α-ketoglutarate as substrate in these tests, carbon dioxide was produced by slices and homogenates of the control tissues, but not by those of the maple syrup urine case. This was of interest in view of the failure of the latter tissues to form succinate from pyruvate.

Experiments designed to show the possible formation of coenzyme A intermediates of leucine metabolism below the level of α-ketoisocaproate were unsuccessful in all cases. The substrates used were leucine-pyruvate, α-ketoisocaproate, and isovaleryl-S-CoA, supplied with all known cofactor requirements.

Discussion

The most prominent feature of the aminoaciduria of maple syrup urine disease is the marked increase in the amounts of leucine, isoleucine and valine, and it is now well established that this results from high levels in the blood (Dancis *et al.*, 1960). This suggests a block in the intermediary metabolism of these amino acids, and the demonstration by the above authors of normal transamination in a variety of tissues, and of the excretion of large amounts of the keto acid analogues of the branched-chain amino acids (Menkes, 1959), has indicated that the block occurs at a point below the keto acid level. These results have been confirmed in the present study.

Analyses of the urine and of tissue extracts have failed to detect the presence of free acid or coenzyme A intermediates of further degradation beyond the keto acid stage, suggesting that the defect probably occurs in the oxidative decarboxylation of the keto acids. However, direct demonstration of a deficiency in this process has been prevented by the instability in storage of the enzyme systems concerned. Tests on fresh tissues, preferably obtained at biopsy, may be expected to provide a definite answer to this question when another patient becomes available for study. The above results are summarized in Fig. 1.

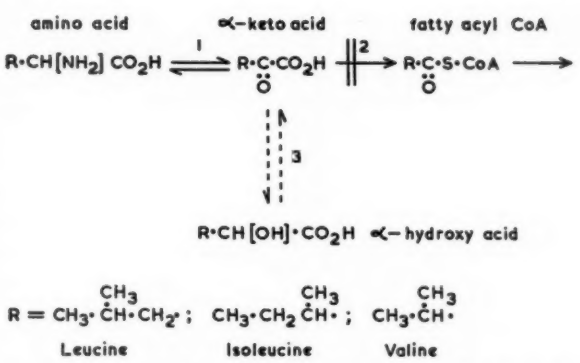

FIG. 1.—Initial steps in the degradation of the branched-chain amino acids. In maple syrup urine disease transamination (reaction 1) occurs normally, but further degradation is prevented by a block in oxidative decarboxylation (reaction 2). This causes the amino and α-keto acids to accumulate, and gives rise to the α-hydroxy acid by-products (reaction 3).

Some evidence of a more general failure of oxidative decarboxylation is seen in the apparent impairment of utilization of pyruvate and α-ketoglutarate by tissue preparations. This situation could arise as the result of a primary defect in the oxidative decarboxylation of a specific keto acid, which then affects similar processes by causing inhibition of some common mechanism. The high concentrations of the branched-chain keto acids may lead to varying degrees of competitive inhibition in this syndrome. In a wider sense, the consequences of such secondary effects may be more serious than those resulting directly from the primary anomaly. A generalized inhibition of oxidative decarboxylation would drastically disrupt the normal functioning of the citric acid cycle, and those tissues having high energy demands, e.g. brain, might be expected to suffer most from this limitation. In view of the early appearance of central nervous system symptoms in this disease, it would be of interest to determine whether the citric acid cycle is already affected at that stage, or whether this occurs only as a result of progressive complication. In this connexion it should be mentioned that previous authors have not reported a raised level of α-ketoglutarate in the urine. Thus, the abnormal level found in this case may have reflected an episode of generalized metabolic failure of the kind outlined above.

The high concentrations of the α-hydroxy acid analogues of the keto acids could also have a direct toxic influence, but again it is possible that secondary effects play an important part in neurochemical disturbances. For example, if the reductive process were normally coupled with oxidative decarboxylation in a DPN-linked system (as occurs in the coupled oxidation-reduction of pyruvate), then a failure by the oxidative process to regenerate reduced DPN could lead to interference in other similarly coupled systems.

However, the most obvious feature of the metabolic disturbance lies with the amino acids them-

selves, and here the normal control of their intracellular distribution may be so deranged by the high local concentrations of leucine, isoleucine and valine, that tissue function becomes seriously impaired. Whatever might be the ultimate connexion between the biochemical lesion and the clinical symptoms, the only course of treatment suggested by the present biochemical studies is the dietary restriction of the branched-chain amino acids.

Work is proceeding in an attempt to identify the substances giving rise to the maple syrup odour. It may be found that such substances are members of a wider group of compounds possessing this characteristic odour, and being derived by similar processes from intermediary acids. Smith and Strang (1958) reported a case in which the urine had a penetrating odour resembling burnt sugar, and found this property to be associated with α-hydroxy-butyric acid. They suggested that the odour was due to an oxidation or polymerization product of the hydroxy acid. Similar products could also be derived from the hydroxy acids occurring in maple syrup urine.

Summary

A case of maple syrup urine disease, with survival to 15 months, is presented. The urine contained high concentrations of leucine, isoleucine and valine, and of their respective keto acids, but other possible intermediates in the further degradation of these amino acids were not detected. The presence of the α-hydroxy acid derivatives of the keto acids was confirmed.

A block in the metabolism of the three amino acids at the stage of oxidative decarboxylation is suggested by these results, but a direct demonstration of this was prevented by the instability of the enzyme systems in storage. Some indications of a more general failure of oxidative decarboxylation were observed, and the possible significance of this and the other anomalies is discussed.

I wish to express my thanks to Dr. Barbara Clayton for her advice and encouragement, and to Mr. A. Whitfield for skilful technical assistance.

I am also grateful to Professor A. Moncrieff for permission to report this case, and to Professor C. E. Dent, Dr. M. Bodian and Dr. Barbara Ockenden for supplying experimental tissues.

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ESSENTIAL BENIGN FRUCTOSURIA

BY

Z. LARON

From the Paediatric Metabolic and Endocrine Clinic and the Rogoff Medical Research Institute, Beilinson Hospital, Petah Tikva, Israel

(RECEIVED FOR PUBLICATION JULY 13, 1960)

Essential fructosuria is a benign inborn error of metabolism characterized by an inability to utilize fructose completely (Hsia, 1959). It was first described in 1876 independently by Zimmer and Czapek (Zimmer, 1876; Czapek, 1876). Sachs, Sternfeld and Kraus in 1942 reviewed 39 proven cases. Since then 10 more cases have been reported (Trivette and Anderson, 1948; Ulgen, 1952/53; Levy, 1953; Faron, 1955; Lenzner, 1956; Cantoni and Klinger, 1957; B. Verbin, 1959, personal communication). Lasker (1941) estimated that fructosuria occurred once in every 120,000 births and supplied evidence that the disturbance was inherited by virtue of an autosomal recessive gene.

In the present paper we wish to report a case of essential fructosuria with a study of the influence of hyper- and hypoglycaemic agents on the fructosuria.

Case Report

A Jewish, Tripoli-born girl, 11½ years of age, was admitted to the hospital on December 28, 1957, suffering from acute rheumatic fever. Her parents and three other siblings were healthy. The family history and the parent's past history were unrevealing. The diagnosis of rheumatic fever was confirmed and she was treated with cortisone and salicylates. During hospital treatment the urine was found positive for sugar on repeated occasions. On a standard hospital diet she excreted 2·5 to 12 g. of sugar per 24 hours. No acetone was found. Fasting blood sugar level was normal and an oral glucose tolerance test (3 g. per kg. body weight) performed after discontinuation of cortisone, showed the following values: Fasting blood sugar, 96 mg./100 ml.; after 30 minutes, 211 mg./100 ml.; after 60 minutes, 150 mg./100 ml.; 120 minutes, 145 mg./100 ml.; 180 minutes, 109 mg./100 ml. Serum total proteins were 7·24 g. %, albumin 4·8 g. %, blood urea 36 mg./100 ml. Liver function tests were normal.

According to the tests listed in the Table and the paper chromatography in Fig. 1, the sugar excreted in the urine was identified as fructose. It was demonstrated by the Lasker test (1941) that abstaining from fructose-containing food prevented the fructosuria. Ingestion of dextrose did not cause fructosuria. Upon ingestion of 50 g. fructose the sugar appeared in the urine within a short time.

Following discharge the patient made an uneventful recovery at home. Further investigations were performed on an ambulatory basis, the body weight of the patient at that time being 40 kg.

Methods

Loading tests were performed after the following preparation: (*a*) supper on the previous evening did not include fruits, vegetables or sugar; (*b*) patient fasted for 14 hours; (*c*) the control urine specimen before the test was sugar-free. The dose of fructose administered was 1 g. per kg. body weight unless otherwise stated.

Total blood sugar was estimated by the method of Rappaport and Eichhorn (1950), blood fructose by the method of Patterson and Herbert as modified by Thompson and others (Behrendt, 1949). Blood dextrose was calculated by subtracting blood fructose from total blood sugar. Urine was collected hourly by indwelling catheter. As the sugar in the urine had been shown to be fructose only, urinary fructose was determined by the method of Fehling, but each specimen was also checked with glucose oxidase paper (Clinistix-Ames). Several urine specimens were examined also by paper chromatography (butanol acetic acid). Serum inorganic phosphorus was measured by the method of Fiske and Subbarow (1925).

Results

Fig. 2 shows the curve of blood fructose concentration in the patient after an oral and intravenous load, as compared to the blood fructose curve in a normal child of the same age after an oral fructose load. It is seen that the blood fructose level in the control subject after the oral fructose load, increases slightly and returns gradually to the fasting level after four hours. In the patient the same oral dose

TABLE

IDENTIFICATION OF URINARY SUGAR

Test	Reaction
Benedict	Positive
Fehling	Positive
Nylander	Positive
Selivanoff	Positive
Glucose-oxidase (Clinistix-Ames-Co)	Negative
Polarimeter	Levorotation

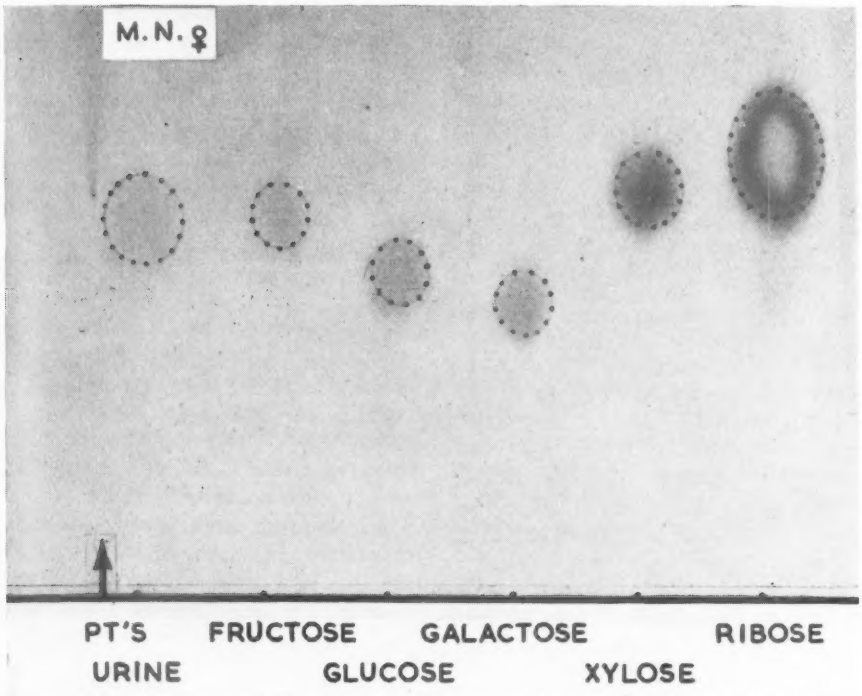

FIG. 1.—Paper chromatography of patient's urine and sugar standards. (Butanol-acetic acid; 16 hours.)

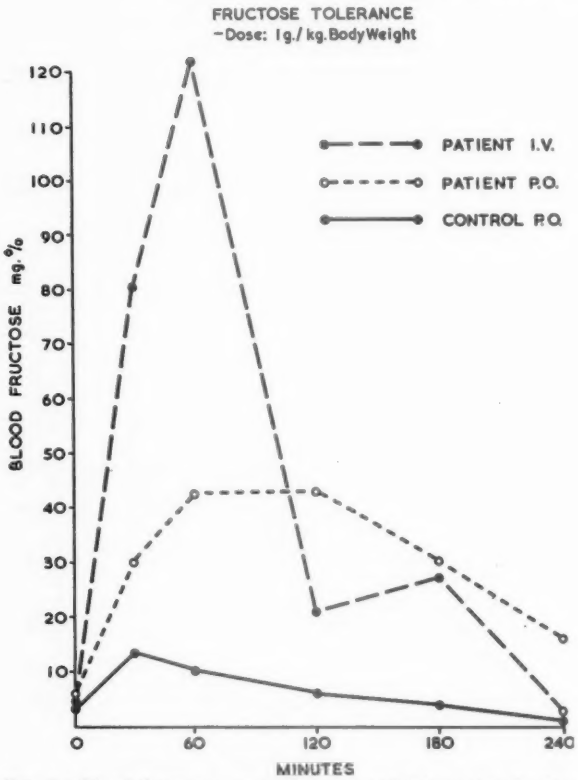

FIG. 2.—Blood fructose curves after oral and intravenous fructose administration to the patient and oral fructose administration to a control subject.

of fructose per unit body weight caused a marked increase in the blood fructose level. Four hours after the start of the test, the concentration was still three times the fasting value. After an intravenous load, given by continuous drip during one hour, a blood fructose concentration of 120 mg. % was reached. A rapid decrease occurred after stopping the infusion and at four hours the normal fasting level was regained. After the oral fructose load in the patient, fructose appeared rapidly in the urine and was excreted during a period of three hours in a total amount of 5·2 g. or 13% of the administered dose (Fig. 3). The highest excretion occurred during the second hour. No fructose appeared in the urine of the control subject. After intravenous administration fructose was excreted by the patient in the urine only during the first two hours (Fig. 4), in a total amount of 5·91 g. or 16% of the dose.

Further fructose loading tests were performed by raising or lowering the blood dextrose concentration. When 60 g. dextrose and 40 g. of fructose were given simultaneously by mouth and the patient's urine and blood examined over a period of four hours, the total blood sugar rose to a maximum of 200 mg. %, representing the sum of dextrose and fructose concentration (Fig. 5), the highest blood fructose concentration being 50 mg./100 ml. Fructose was excreted throughout the four hours of the experiment: 8·8 g. or 21·2% of the fructose load. The

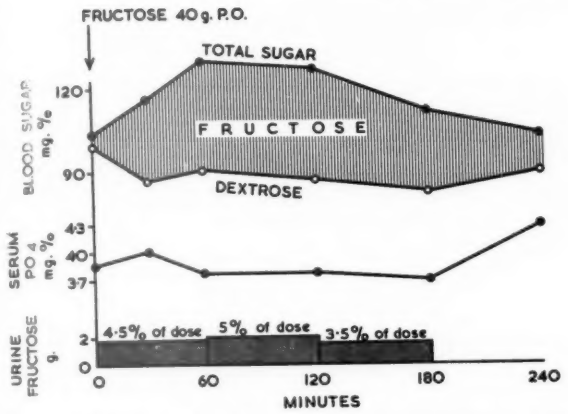

FIG. 3.—Total blood sugar, fructose and dextrose concentrations and urine fructose excretion after an oral fructose load to the patient.

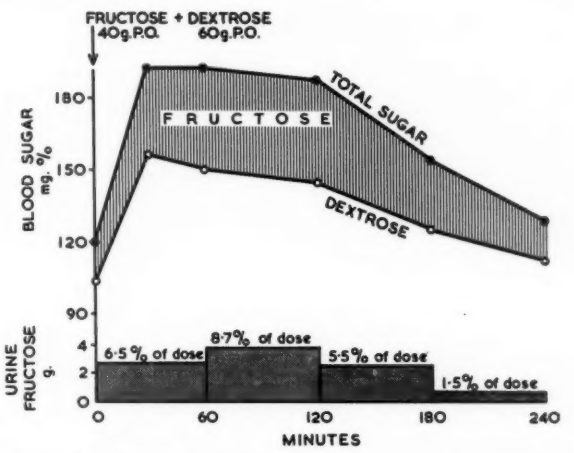

FIG. 5.—Total blood sugar, fructose and dextrose concentrations and urine fructose excretion after a simultaneous oral load of fructose and dextrose.

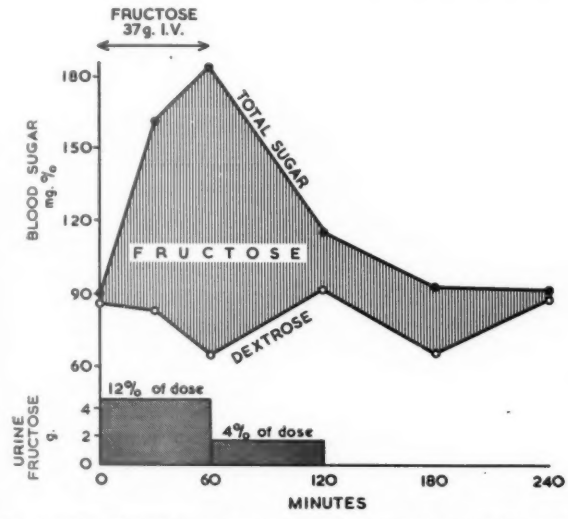

FIG. 4.—Total blood sugar, fructose and dextrose concentrations and urinary fructose excretion after an intravenous fructose load.

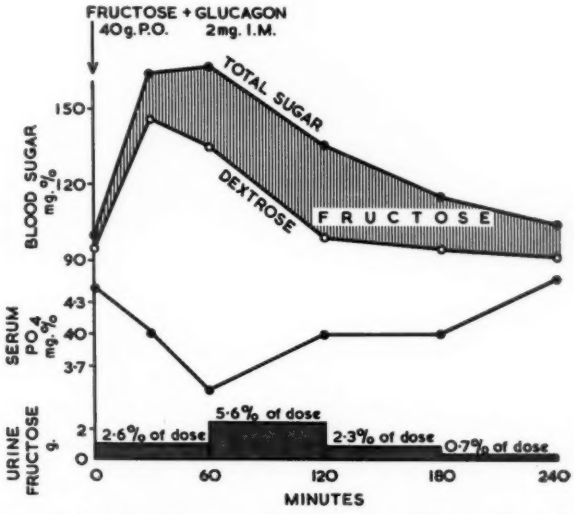

FIG. 6.—Total blood sugar, fructose, dextrose and serum inorganic phosphorus concentrations and urine fructose excretion after an oral fructose load and simultaneous intramuscular injection of glucagon.

maximum excretion occurred in the second hour. No dextrose appeared in the urine.

When hyperglycaemia was induced by the injection of glucagon (2 mg., intramuscularly, Fig. 6), the fructosuria also continued throughout the four hours of the test; 4·46 g. corresponding to 11% of the load were excreted, with the maximum excretion in the second hour. No dextrose appeared in the urine.

Lowering the blood dextrose concentrations by either insulin (4 units intravenously, Fig. 7), or by tolbutamide (2 g. given by mouth, Fig. 8), the blood fructose curve was similar to that obtained with oral fructose alone, but the quantity of fructose excreted in the urine over three hours was smaller: 2·4 g., corresponding to 6% of the load in both instances.

An intravenous injection of 250 mg. hydrocortisone did not influence the blood fructose levels nor urine fructose excretion after an oral fructose load.

In order to determine the maximum amount of fructose which our patient was capable of metabolizing, intravenous infusions of fructose of different concentrations were given at a constant rate and the urine tested for the appearance of sugar. When a 1% solution was infused over one hour, so as to deliver 40 mg. fructose per minute, no sugar appeared in the urine. When a 2% solution of fructose was infused, so as to deliver 60 mg. fructose per minute, there was reduction

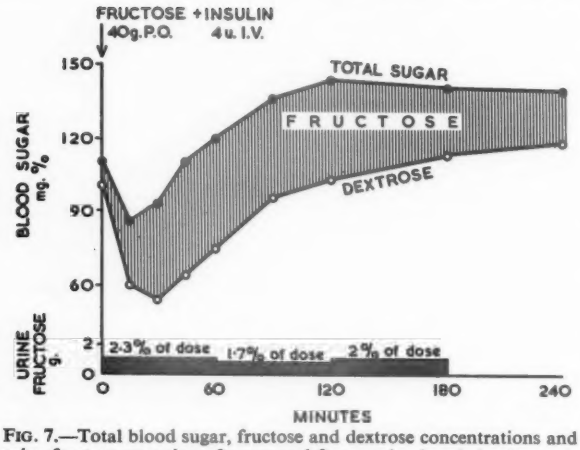

FIG. 7.—Total blood sugar, fructose and dextrose concentrations and urine fructose excretion after an oral fructose load and simultaneous intravenous injection of insulin.

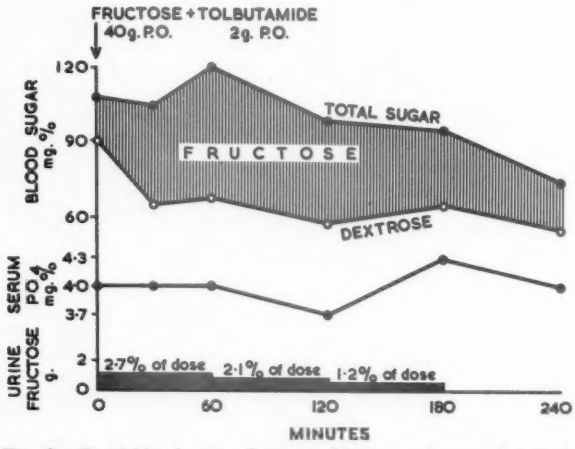

FIG. 8.—Total blood sugar, fructose, dextrose and serum inorganic phosphorus concentrations and urine fructose excretion after an oral fructose load and simultaneous tolbutamide administration.

of Nylander solution by the urine during the period of infusion and for one hour after its termination. The excretion of fructose was confirmed by chromatography and polarimetry. The Fehling and bicarbonate test remained negative throughout, indicating that the quantity of fructose excreted as a result of this load was very small, such as to be detected only by sensitive tests.

Upon examining the relationship of blood fructose and dextrose concentrations in the simple and double loading tests performed (Figs. 3-8), it is seen that blood fructose concentrations were not influenced by changes in blood dextrose. When fructose was administered alone (Figs. 3 and 4), a slight drop of the blood dextrose concentration was observed initially. Serum inorganic phosphorus concentration, usually, but not always, varied inversely with the blood dextrose level.

The urine of the patient's three siblings, her grandparents, parents, uncles and aunts and he latter's children was repeatedly tested after a fructose load (honey). Fructosuria was never detected.

Discussion

In the normal individual fructose is metabolized at a faster rate than glucose (Albanese, Fel:h, Higgons, Vestal and Stephanson, 1952; Mendel:off and Weichselbaum, 1953). In liver disease th:re is a disturbance in fructose metabolism which m ay lead to the excretion of this sugar in the ur ne (Strauss, 1901 (cited by Steinitz, 1939); Stein tz, 1937). Recently we have reported the occurrence of fructose among other sugars in the urine of a baby suffering from the nephrotic syndrome (Laron, Yonis, Tissibov and Boss, 1960).

In the past 85 years, 50 cases (including the present one) of otherwise normal individuals who excreted fructose in the urine have been described (Sachs *et al.*, 1942; Trivette and Anderson, 1948; Ulgen, 1952/53; Levy, 1953; Faron, 1955; Lenzner, 1956; Cantoni and Klinger, 1957; B. Verbin, 1959, personal communication). As this was a symptomless manifestation, the finding was incidental and was made at different ages. In some instances it occurred in father and child or in siblings. Considering the present routine to test urine for sugar with paper strips impregnated with glucose oxidase, cases of essential benign fructosuria are likely to be overlooked, and the incidence therefore may be higher than reported. The proportion of Jews in the known and proven cases of this disorder is high, constituting 18 out of 50 cases.

It is assumed that the pathogenesis of essential benign fructosuria is due to a congenital lack of the hepatic enzyme fructokinase which catalyses the conversion of fructose to fructose 1-PO_4 (Renold and Thorn, 1955). In all of the cases of essential benign fructosuria reported, it was observed that only about one-tenth of the fructose load is excreted in the urine. It can be inferred, therefore, that besides the pathway mediated by fructokinase there must be alternative ways for the utilization of fructose. Evidence for this is the demonstration of conversion of fructose to fructose 6-PO_4 in the presence of hexokinase and ATP in the brain and muscles (Slein, Cori and Cori, 1950). The inhibitory action of glucose on the phosphorylation of fructose by hexokinase (Renold and Thorn, 1955), may explain why the addition of dextrose in earlier studies (Steinitz, 1931; Silver and Reiner, 1934) and in the present one was accompanied by prolonged fructosuria and excretion of a larger amount of fructose. The action of glucagon prolonging the

period of fructosuria without increasing the total amount of sugar excreted, may be explained by the lesser degree of hyperglycaemia caused by the drug, as compared to that following a combined dextrose and fructose load. Whether the decreased fructose excretion during the hypoglycaemia induced by insulin or tolbutamide, is due to greater availability of hexokinase in the tissue, is hypothetical. The ineffectiveness of insulin on the fructosuria noted by Silver and Reiner (1934), may have been due to the different route of administration and possibly less marked hypoglycaemia. In our patient about 50 mg. of fructose per minute could be metabolized by the alternative pathway, as found in experiments with constant intravenous infusion of fructose.

In recent years a malignant form of fructosuria has been described by Chambers and Pratt (1956) and Froesch, Prader, Wolf and Labhart (1959). This 'hereditary fructose intolerance' characterized by severe hypoglycaemia occurring upon ingestion of fructose was shown to be caused by a lack of the enzyme 1-phospho-fructaldolase.

Summary

A case of essential benign fructosuria in an 11-year-old Jewish girl is described.

Both hyperglycaemia induced by administration of dextrose or glucagon and hypoglycaemia induced by administration of insulin or tolbutamide affected the duration and/or the amount of fructose excreted in the urine after a fructose load.

The patient was able to metabolize up to 50 mg. of fructose per minute. Any amount in excess was excreted in the urine.

These findings are discussed in the light of the enzymatic disturbances invoked in this metabolic disorder.

The author is indebted to Mrs. F. Eichhorn and Dr. F. Rappaport (deceased) of the Laboratory of Clinical Chemistry for performing the paper chromatography and the polarimetric tests. Glucagon was kindly supplied by Dr. W. R. Kirtley of the Eli Lilly Research Laboratories, Indianapolis, U.S.A. During hospital treatment the patient was under the care of Drs. Z. Yonis and M. Gefman.

Prof. A. de Vries gave helpful criticism during the preparation of the paper.

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HYDROGEN CONCENTRATION, CARBON DIOXIDE TENSION AND ACID BASE BALANCE IN BLOOD OF HUMAN UMBILICAL CORD AND INTERVILLOUS SPACE OF PLACENTA

BY

G. ROOTH, S. SJÖSTEDT and F. CALIGARA

From the Departments of Obstetrics and Gynaecology and Internal Medicine, University Hospital, Lund, and the Wenner-Gren Cardiovascular Research Laboratory, Norrtull Hospital, Stockholm, Sweden

(RECEIVED FOR PUBLICATION JUNE 23, 1960)

In a previous paper (Sjöstedt, Rooth and Caligara, 1960) we reported on the oxygen tension (pO_2) in the blood of the human umbilical cord and the intervillous space of the placenta. It is the purpose of this paper to report on the *p*H and the carbon dioxide tension (pCO_2) in blood from the same sources in order to give a more complete picture of the gas exchange of the foetus and of its acid base balance.

Material and Methods

The cord blood was investigated in 222 cases after spontaneous delivery in vertex presentation; 154 of the infants were normal and without any signs of asphyxia before or after delivery; 46 had signs of asphyxia and 33 of these had slow or irregular heart beats during delivery but showed no signs of asphyxia after birth. The other 13 cases had signs of mild asphyxia after birth. In addition, 22 infants had meconium stained amniotic fluid without any other signs of asphyxia.

During labour the mothers were given 'trilene' (trichlorethylene) or nitrous oxide and in some cases a few drops of chloroform at the moment of delivery.

The blood in the intervillous space was investigated in 27 cases, 25 of which were normal and two of which had signs of mild toxaemia. The placenta was punctured through the abdominal wall before labour had started. Only local anaesthesia was used for the puncture and no complications occurred. The technique of the puncture has been described earlier by us (Sjöstedt *et al.*, 1960).

Great care was taken to obtain reliable information about the time of gestation. Any case in which the duration of pregnancy was doubtful was rejected from the series on the effect of gestation time upon the *p*H, pCO_2 or pO_2 of the blood.

The pO_2 was measured polarographically with the Clark electrode as described by us (Rooth, Sjöstedt and Caligara, 1959a).

The *p*H was measured with a radiometer type 22 *p*H meter and an Astrup apparatus. The temperature was kept at 37·0° C.

The pCO_2 was measured by the Astrup method (1956). The principle is that the *p*H of the whole blood is first measured anaerobically. After centrifugation, the plasma is equilibrated with a gas of known pCO_2 (close to 40 mm. Hg) and the *p*H is again measured. The pCO_2 of the whole blood is then read off from the nomogram of Astrup (1956).

Standard bicarbonate buffer base (BB) and base excess (BE) are all terms which express the metabolic acid-base balance of the blood. In order to calculate those entities we used the nomogram of Siggaard Andersen and Engel (1960). Instead of measuring the haemoglobin in our cord blood we used a mean of 16·7 g./100 ml. blood, a figure which was established in a previous study on 414 cord samples in this laboratory (Rooth and Sjöstedt, 1957b). This introduces an error in the calculations which, if the haemoglobin varies ±4 g./100 ml. blood from 16·7 g., will make about ±1·3 mEq/litre in BB, but scarcely any error in BE and standard bicarbonate.

As the cord blood contains a considerable amount of reduced haemoglobin which is more alkaline than oxyhaemoglobin, this must be taken into account and we have used the correction given by Siggaard Andersen and Engel (1960) according to which 10 g. of reduced haemoglobin increases the BB 0·3 mEq. The oxygen saturation has been calculated from the *p*H and pO_2 measurements with the help of the dissociation curve for the foetal blood established by us (Rooth *et al.*, 1959b).

BB is the buffering protein of the blood + buffering bicarbonate. Henderson (1928) used this as an indicator of the metabolic acid base balance of the blood, but the term BB was introduced by Singer and Hastings (1948).

Standard bicarbonate is another indicator of the metabolic status introduced by Astrup (1956) and Jørgensen and Astrup (1957). Standard bicarbonate is the concentration of bicarbonate in plasma, when whole

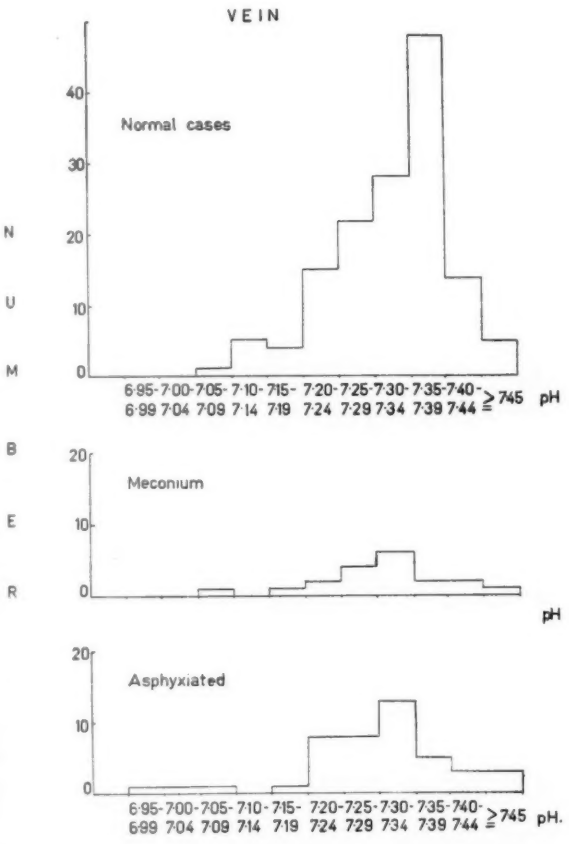

FIG. 1.—Distribution of the *p*H in the umbilical vein in normal and asphyxiated infants and infants with meconium stained amniotic fluid.

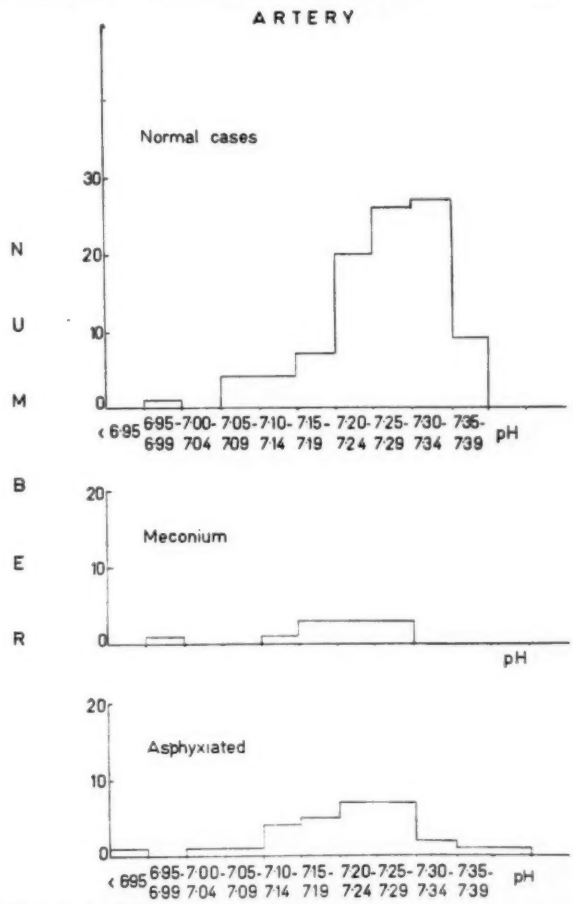

FIG. 2.—Distribution of the *p*H in the umbilical arteries in normal and asphyxiated infants and infants with meconium stained amniotic fluid.

blood has been equilibrated with carbon dioxide at a pCO_2 of 40 mm. Hg at 38° C. and when the haemoglobin is fully oxygenated. The carbon dioxide-bicarbonate systems account for about 75% of the buffering action of the blood against fixed acid and bases.

BE is the same as normal BB minus the actual BB. The term BE was introduced by Astrup, Jørgensen, Siggaard Andersen and Engel (1960). Consequently BE directly expresses the excess in mEq of strong base or acid for every litre of blood, when the normal mean is arbitrarily fixed at zero. For the discussion of the relative merits of these different entities the reader is referred to the work of Astrup *et al.* (1960).

Results

Cord Blood

HYDROGEN CONCENTRATION. The *p*H in the umbilical vein in 142 normal cases and in the arteries in 8 cases is given in Figs. 1 and 2. These figures also give the *p*H in the vein of 44 cases grouped as asphyxiated and 30 measurements from the arteries in the same group. Finally they also show the *p*H of the cases with meconium stained amniotic fluid. In this group measurements have been done in 18 cases in the vein and in 11 cases in the umbilical artery.

It will be observed that the *p*H is lower in the asphyxiated and meconium groups than in the normal cases (see also Table 2). In the normal ones, 54% of the cases have a *p*H in the vein which is lower than 7·35. In the meconium group this percentage is 72 and in the asphyxiated group 75. In the arteries the *p*H is lower than 7·25 in 37% of the normal cases, in 73% of the meconium group and in 63% of the asphyxiated group

Table 1 gives the *p*H and pO_2 in the normal cases for different gestation weeks. The material has been divided into primigravidae and multigravidae. It will be seen that the *p*H may decrease in the umbilical arteries and vein when the gestation time is 42 weeks or more, but pO_2 does not change with

TABLE 1

MEAN HYDROGEN CONCENTRATION, CARBON DIOXIDE AND OXYGEN TENSION IN THE UMBILICAL CORD BLOOD AFTER NORMAL DELIVERY IN DIFFERENT GESTATION WEEKS

		Gestation Week								
		36	37	38	39	40	41	42	43	All
Artery:										
Primigravidae	*p*H ..	7·27		7·27	7·22	7·25	7·26	7·28	7·24	7·25
	No. ..	2		2	8	16	9	4	5	46
	pCO_2 ..	30			44	47	45	41	57	44
	No. ..	1			3	5	2	3	1	15
	pO_2 ..	24		19	21	19	19	23	19	20
	No. ..	2		2	9	15	6	8	7	49
Multigravidae	*p*H ..		7·34	7·30	7·26	7·29	7·29	7·21	7·19	7·27
	No. ..		1	2	3	16	13	7	3	45
	pCO_2 ..				38	45	51	57	49	47
	No. ..				2	6	3	1	1	13
	pO_2 ..		31	27	18	16	16	14	14	16
	No. ..		1	1	4	18	11	9	4	48
All	*p*H ..	7·27	7·34	7·29	7·23	7·26	7·28	7·23	7·22	7·26
	No. ..	2	1	4	11	32	22	11	8	91
	pCO_2 ..	30			41	46	49	45	53	45
	No. ..	1			5	11	5	4	2	28
	pO_2 ..	24	31	22	20	17	17	19	17	18
	No. ..	2	1	3	13	33	17	17	11	97
Vein:										
Primigravidae	*p*H ..	7·32		7·33	7·31	7·31	7·32	7·30	7·28	7·31
	No. ..	2		3	9	19	12	8	9	62
	pCO_2 ..	27		29	37	39	43	38	39	38
	No. ..	1		2	4	7	3	4	5	26
	pO_2 ..	34		31	30	29	29	33	30	30
	No. ..	2		2	11	18	7	9	8	57
Multigravidae	*p*H ..	7·38	7·40	7·34	7·33	7·35	7·36	7·31	7·27	7·34
	No. ..	1	1	3	6	23	20	9	4	67
	pCO_2 ..	33		38	37	36	34	43	48	37
	No. ..	1		2	3	8	6	2	2	24
	pO_2 ..	33	43	33	27	27	31	26	30	28
	No. ..	1	1	2	7	23	19	11	4	68
All	*p*H ..	7·34	7·40	7·34	7·32	7·33	7·35	7·31	7·27	7·32
	No. ..	3	1	6	15	42	32	17	13	129
	pCO_2 ..	30		33	37	38	37	40	41	38
	No. ..	2		4	7	15	9	6	7	50
	pO_2 ..	34	43	32	29	28	30	29	30	29
	No. ..	3	1	4	18	41	26	20	12	125

TABLE 2

MEAN OXYGEN TENSION, HYDROGEN CONCENTRATION, CARBON DIOXIDE TENSION, STANDARD BICARBONATE, BUFFER BASE AND BASE EXCESS IN THE UMBILICAL CORD BLOOD AFTER NORMAL DELIVERY OR AFTER DELIVERY WITH DIFFERENT SIGNS OF ASPHYXIA

	pO_2 (mm. Hg)	No.	*p*H	No.	pCO_2 (mm. Hg)	Standard Bicarbonate	Buffer Base (mEq/litre)	Base Excess	No.
Artery:									
Normal cases	18·3	104	7·26	98	45	14·8	34·7	−12·2	25
Slow or irregular heart beats before delivery	17·6	21	7·21	22	55	16·2	36·7	−10·2	12
Meconium stained amniotic fluid	16·4	14	7·20	11	51	10·8	27·6	−19·4	2
Asphyxiated after delivery ..	14·5	7	7·16	8	39	12·9	31·9	−15·1	2
Vein:									
Normal cases	29·2	137	7·33	142	38	17·6	39·2	− 7·7	6
Slow or irregular heart beats before delivery	28·9	31	7·31	31	41	18·0	39·8	− 7·1	20
Meconium stained amniotic fluid	28·4	18	7·30	18	44	15·8	36·3	−10·6	16
Asphyxiated after delivery ..	27·6	11	7·24	13	44	14·6	34·1	−13·9	5

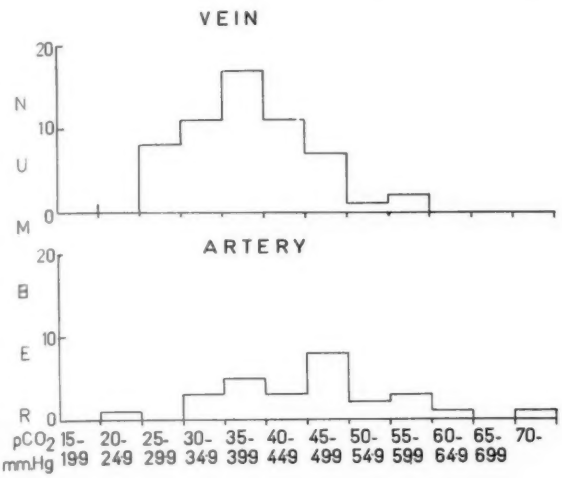

FIG. 3.—Distribution of the pCO_2 in the umbilical vein and arteries of normal infants.

advancing gestation time, a fact which has been shown by us previously (Sjöstedt *et al.*, 1960). There is also a tendency for the *p*H to be lower in primigravidae than in multigravidae.

CARBON DIOXIDE TENSION. The distribution of the pCO_2 values in the cord blood of the normal cases is shown in Fig. 3. The mean values of pO_2, *p*H and pCO_2 are given in Table 2 for the normal cases and the groups with various signs of asphyxia. The first group had slow or irregular heart beats before the delivery, but no signs of asphyxia after birth. The second group had meconium stained amniotic fluid, but no other signs of asphyxia before or after birth. The third group showed signs of asphyxia after the delivery, manifested by diminished muscular tonus and/or delayed onset of spontaneous respiration. No case of severe asphyxia was studied in this series.

It will be observed that pCO_2 in the umbilical arteries and vein is higher in the asphyxiated than in the normal cases. The asphyxiated cases also have reduced pO_2 and *p*H. The changes are of about the same magnitude in the arteries and the vein though perhaps a little more pronounced in the arteries.

Although the number of observations in the different gestation weeks is small there seems to be an increase of the pCO_2 in the umbilical vein blood with advancing gestation. No such increase can be observed in the arteries.

ACID BASE BALANCE. The distribution of the standard bicarbonate and BB in 56 normal cases from the vein and in 25 normal cases from the arteries is given in Fig. 4. The mean values for the metabolic acid base balance are shown in Table 2. The number of pathological cases is small especially in the arteries. There is a metabolic acidosis in the infants asphyxiated after birth and in those with meconium stained amniotic fluid.

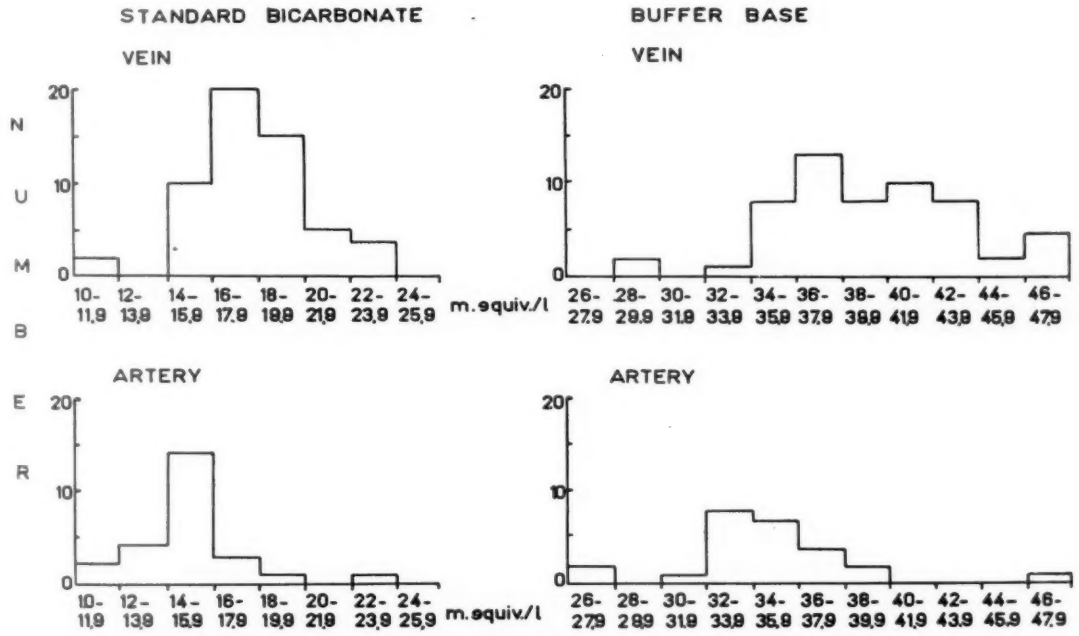

FIG. 4.—Distribution of standard bicarbonate and buffer base in the vein and arteries of normal infants.

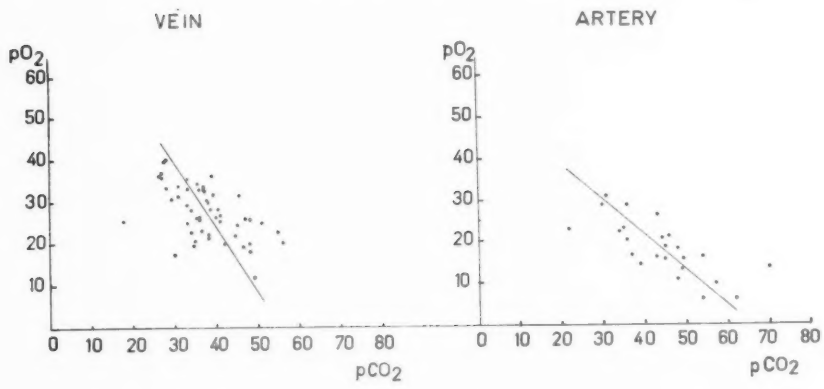

FIG. 5.—The relation between pCO_2 and pO_2 in the umbilical vein and arteries of normal infants.

The relation between the pO_2 and pCO_2 in the umbilical vein and arteries is given in Fig. 5. It will be seen that if the pO_2 decreases, the pCO_2 increases, as would be expected in any situation which obstructs the normal passage of gas from the mother and vice versa.

Intervillous Blood of the Placenta. The figures for the pO_2, *p*H, pCO_2 and the metabolic acid base balance in 27 samples from the intervillous blood of the placenta are given in Table 3. Compared with the umbilical blood, the intervillous blood has higher pO_2, *p*H, standard bicarbonate and BB. The pCO_2 is lower than in the umbilical artery and the same as in the umbilical vein.

Discussion

Hydrogen Concentration. The present investigation corroborates and extends knowledge about the *p*H of the cord blood. A detailed discussion of earlier works has recently been published by Kaiser (1959). Table 4 shows the *p*H values available in the literature after 1932.

These studies have established that the *p*H of the umbilical arteries is lower than that of the umbilical vein. The *p*H of the umbilical vein in its turn is lower than that of the maternal vein and artery. In this respect it is perhaps better to make a comparison with the *p*H of the intervillous blood, which we have found to be 7·41 against 7·33 for the

TABLE 3

OXYGEN TENSION, HYDROGEN CONCENTRATION, CARBON DIOXIDE TENSION, STANDARD BICARBONATE, BUFFER BASE AND BASE EXCESS IN THE INTERVILLOUS BLOOD OF THE PLACENTA

Case	pO_2 (mm. Hg)	*p*H	pCO_2 (mm. Hg)	Standard Bicarbonate	Buffer Base (mEq/litre)	Base Excess
1	36					
2	30	7·37				
3	30	7·32				
4	43	7·35				
5	54	7·45				
6	36	7·42				
7	48	7·41				
8	34	7·40				
9		7·33				
10	33	7·39				
11		7·44				
12	36	7·36	43	22	44	−1
13	51	7·43	38	24	47	+2
14	38	7·41	38	23	45	0
15	48	7·39	27	18	38	−7
16	46	7·43	29	20	41	−4
17	35	7·42	48	28	51	+7
18	48	7·40	43	25	47	+3
19	28	7·39	48	25	49	+3
20	48	7·40	36	22	45	−1
21	50	7·40	38	23	45	0
22	35	7·39	34	20	42	−4
23	40	7·43	38	23	45	−1
24	41	7·44	34	23	46	0
25	37	7·45	38	25	49	+3
26	45	7·47	37	26	52	+4
27	37	7·44	38	25	47	+2
Mean	40	7·41	38	23·2	45·8	+0·3
Mean umbilical artery ..	18	7·26	45	14·8	34·7	−12·2
Mean umbilical vein ..	29	7·33	38	17·6	39·2	−7·7

TABLE 4

SURVEY OF UMBILICAL CORD BLOOD *pH* STUDIES

Author	Artery		Vein	
	pH	No.	*pH*	No.
Normal cases:				
Eastman (1932)	7·33	3	7·36	8
Noguchi (1937)	7·32	14	7·36	14
Kaiser (1953)	7·26	12	7·32	12
Goodlin and Kaiser (1957)	7·28	28	7·32	28
James *et al.* (1958)			7·26	30
Kaiser and Goodlin (1958)			7·34	25
MacKinney *et al.* (1958)			7·29	200
Wulf (1959a)			7·35	40
Wulf (1959b)	7·30	36	7·41	36
Present series	7·26	98	7·33	142
Asphyxiated cases:				
Eastman (1932)			7·04	6
Noguchi (1937)			7·24	7
James *et al.* (1958)	7·04	10		
Wulf (1959)	7·18	20	7·23	20
Present series	7·20	41	7·29	62

umbilical vein. It will be seen from Fig. 1 that there are more cases with a *p*H between 7·35 and 7·40 than in any other group. Thus the *p*H difference between the intervillous maternal blood and the umbilical vein is small in normal cases. The *p*H of foetal blood increases during its passage through the placenta, indicating that this blood is giving up carbon dioxide and/or fixed acids. This will be discussed later.

The highest mean *p*H values in the umbilical vein given in the literature are those of Wulf (1959b), Eastman (1932) and Noguchi (1937). Wulf gives the high value of 7·41 and the others give 7·36. Noguchi also has the highest value in the umbilical artery, i.e. 7·32. The largest series (MacKinney, Goldberg, Ehrlich and Freymann, 1958) consisting of 200 cases before respiration has a mean of only 7·29. Most of the investigators have a mean of about 7·32. These variations are probably due, in the main, to differences in technique, particularly in the *p*H standard, and in material. If the *p*H is high and the technique sound, this indicates that the cases are normal and the *p*H values represent the true intrauterine figures.

Kaiser (1959), in his review, states that no information is available about alkalosis in the umbilical cord blood. It is true that the figures so far discussed are those of a mild acidosis. It must be remembered, however, that this expression is used solely because the *p*H is lower than the conventionally given figure for adult arterial blood and that the term acidosis in this sense has no pathological significance. As seen from Fig. 1, in 24 venous samples we have found a *p*H of 7·40 and above. In comparison with the mean *p*H of the umbilical vein this may be called alkalosis. In 40 normal cases Wulf (1959a) found eight with a *p*H higher than 7·40, i.e. about 20% of the total cases, as in the present series. The foetus cannot decrease its pCO_2 and thereby increase the *p*H as the respiring individual does. The only way for the foetus to achieve this is if the pCO_2 of the intervillous blood decreases, i.e. by hyperventilation of the mother. This also occurs during labour and values of arterial maternal pCO_2 of less than 30 mm. Hg have been found by Boutourline-Young and Boutourline-Young (1956) and Weisbrot, James, Prince, Holaday and Apgar (1958).

If the infant is asphyxiated the *p*H is reduced in the umbilical arteries and vein. This decrease in *p*H is first seen in the arteries (Table 2). In the umbilical vein the *p*H is reduced particularly in those cases showing definite signs of asphyxia after birth. The *p*H is then about 0·1 units lower than the normal mean. As seen in Table 4, Eastman (1932) and James, Weisbrot, Prince, Holaday and Apgar (1958) report much lower values. The reason is that these authors analysed cases with severe asphyxia, whereas our cases were only mild. A few of our asphyxiated infants as well as a few of our normal infants have shown very low *p*H values (Figs. 1 and 2). Very low values even in vigorous infants have also been found in cord blood oxygen saturation studies and have been discussed earlier by us (Rooth and Sjöstedt, 1957a).

As seen in Table 1, there is a tendency for the *p*H to be lower in the cord blood of the primigravidae than in that of the multigravidae. As the pCO_2 is the same, this could be explained by more difficult labour during which the mother and/or the foetus has increased production of lactic acid and other fixed acids.

Carbon Dioxide Tension. Tables 5 and 6 give a survey of some pCO_2 and oxygen saturation values available in the literature. A survey of pO_2 values has earlier been given by us (Sjöstedt *et al.*, 1960). It can be seen from these Tables that our material, whether earlier or from the present series, shows high pO_2 or oxygen saturation values and low pCO_2 values. Our *p*H values are of the same magnitude as those established by others, suggesting that our cases are perhaps nearer to normal than those studied by others. This has a special interest in view of the fact that many authors are very cautious about figures obtained from cord blood drawn after delivery. The higher the pO_2 and oxygen saturation and the lower the pCO_2 the higher the probability that the figures represent the original intrauterine conditions. It seems reasonable to assume that the true intrauterine level for the pCO_2 is about 40 mm. Hg for the umbilical artery.

TABLE 5
SURVEY OF UMBILICAL CORD BLOOD pCO_2 STUDIES

Author	Artery		Vein	
	pCO_2 (mm. Hg)	No.	pCO_2 (mm. Hg)	No.
Haselhorst and Stromberger (1931)	50	4		
Eastman (1932)	42	3	36	8
Beer *et al.* (1955)	60	20	45	20
Goodlin and Kaiser (1957)	53	11	42	11
James *et al.* (1958)	55	27		
MacKinney *et al.* (1958)			48·5	189
Wulf (1959a)			44	40
Wulf (1959b)	49	36	44	36
Present series	45	27	38	58

TABLE 6
SURVEY OF UMBILICAL CORD BLOOD OXYGEN SATURATION STUDIES

Author	Artery		Vein	
	Oxygen Saturation	No.	Oxygen Saturation	No.
Eastman (1932)	16	15	50	15
Clemetson and Churchman (1953)	31	10	63	12
Walker (1954)	20	9	48	10
MacKinney *et al.* (1958)	24	234	48	286
MacKay (1957)	30	112	64	112
Rooth and Sjöstedt (1957a)	34	172	62	225
James *et al.* (1958)	22	43	49	55

The arteriovenous difference in pCO_2 of about 7 mm. Hg is a measure of the carbon dioxide given up to the maternal circulation in the placenta. In 26 cases we have found the pCO_2 of the intervillous blood of the placenta to be on an average 40 mm. Hg or identical with that of the foetal pCO_2 of the umbilical vein. These figures indicate an almost complete exchange of CO_2 across the placenta as opposed to the oxygen transport. The difference in pO_2 is about 10 mm. Hg (Sjöstedt *et al.*, 1960). These differences between oxygen and carbon dioxide are to be expected from the higher diffusion coefficient for carbon dioxide.

No previous comparison seems to have been made between the intervillous pCO_2 and the pCO_2 of the foetal circulation in man. Beer, Bartels and Raczkowski (1955) assume for their calculations a complete equilibration. In animals with a syndesmochorial placenta five layers thick such as cows and sheep, pressure differences of about 20 mm. Hg have been found (Roos and Romijn, 1940). In rabbits with a haemoendothelial placenta, Young (1952) has observed values between 14 and −2 mm. Hg.

Darling, Smith, Asmussen and Cohen (1941) calculated the relation between *p*H and pO_2 if the *p*H of the foetal blood is changed by varying the pCO_2. Consequently there is a relation between pCO_2 and pO_2 and this is evident also from Fig. 5. There is a large scatter in these figures as might be expected because we are dealing with individual blood samples and not systematic pCO_2 or pO_2 changes in one and the same blood. It will be observed, however, that even when pCO_2 rises to high levels, the pO_2 is usually maintained, although at a relatively low level. As a rule these cases have a metabolic acidosis and they demonstrate how the pO_2 is kept up at all costs.

Acid Base Balance. Compared with the mother the foetus has a metabolic acidosis (Table 3) and it can be seen that in comparison with the umbilical vein, the umbilical artery has a metabolic acidosis (Table 3 and Fig. 4). Expressed in BB the mean difference between the arteries and the vein is about 4·5 mEq/litre. This difference is a measure of the fixed acids which pass from the foetal to the maternal circulation. Once pulmonary ventilation starts after birth the BB of the arteries and the veins is similar to that in adult blood. Because of the error inherent in our way of estimating the metabolic acid base balance, the present series cannot be used for an exact determination of the normal values in cord blood, but the values are of the same order as those of James *et al.* (1958).

As already shown by Eastman (1932) the slightly asphyxiated foetus compared with the normal foetus has no metabolic acidosis, whereas those with more pronounced asphyxia have low bicarbonate content as a sign of metabolic acidosis. These findings are confirmed and expressed in the more exact form of BB by James *et al.* (1958). Our material is small but the same tendency is present.

Summary

The cord blood of 222 infants has been analysed for *p*H, pCO_2, pO_2 and metabolic acid base balance expressed as standard bicarbonate, BB and BE.

From the placenta 26 samples of intervillous blood have been analysed in the same way and the results are compared with the cord blood in order to show the gas exchange of the foetus.

The mean *p*H after normal delivery is 7·26 in the umbilical artery and 7·33 in the umbilical vein.

The mean pCO_2 after normal delivery is 45 mm. Hg in the umbilical artery and 38 mm. Hg in the vein.

The mean BB after normal delivery is 35 mEq/litre in the umbilical artery and 39 mEq/litre in the vein, indicating that during the passage through the placenta the foetal blood gives up fixed acids to the maternal circulation.

In the intervillous blood of the placenta the mean pH is 7·41, the mean pCO_2 38 mm. Hg and the mean BB 46 mEq/litre.

The pCO_2 in the umbilical vein and the intervillous space of the placenta are the same, 38 mm. Hg, indicating an almost complete exchange of carbon dioxide between the foetal and maternal circulation.

This study was supported by grants from the Association for the Aid of Crippled Children, New York, U.S.A., the Swedish Medical Research Council, Uppsala and Svenska Nationalföreningen mot tuberkulos och andra folksjukdomar, Stockholm, Sweden.

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THROMBI IN THE HEPATIC SINUSOIDS OF THE NEWBORN AND THEIR RELATION TO PULMONARY HYALINE MEMBRANE FORMATION

BY

T. WADE-EVANS

From the Departments of Pathology and Obstetrics, University of Manchester

(RECEIVED FOR PUBLICATION AUGUST 15, 1960)

An increase in the degree of fatty change of the liver was found by Benitez (1952) in babies who had aspirated vernix caseosa or who had pulmonary hyaline membranes, but little else has been recorded about hepatic lesions in such cases. The observation of small thrombi in the sinusoids of the livers of babies with hyaline membranes was thus of interest; the investigation reported in this paper was undertaken to determine the general incidence of such sinusoidal thrombi in stillbirths and in babies dying in the neonatal period, and to examine their relation to pulmonary hyaline membrane formation. In addition, a survey was made of livers taken at autopsy from adult patients, in a smaller proportion of whom similar thrombi are found; Popper and Schaffner (1957) review reports of the occurrence of sinusoidal thrombi in eclampsia, although, as will be shown, these may occur where there is similar circulatory disturbance or focal necrosis of any cause.

Observations and Methods

The thrombi within the sinusoids of the liver are difficult to detect in sections stained by haematoxylin and eosin, but they stain prominently as fibrin with phosphotungstic-acid haematoxylin or the picro-Mallory method. The latter gives the better colour contrast between thrombi and erythrocytes or parenchymal cells and was used on all the material we examined. The method of McFarlane (1944) was slightly modified to suit the formalin fixed tissue available.

The thrombi are small, being sometimes formed of separate strands of fibrin but more often compact and rounded, as if moulded by the blood stream (Fig. 1). They are usually single, but may form groups of two or three, and less often up to five or six. They are not confined to any one zone of the liver lobule. They are discrete, and are not continuous with thrombus in the larger vessels of the liver; although observations on the main portal, hepatic or umbilical veins, and on the hepatic artery were not recorded, examination of the sections shows thrombus to be uncommon in the branches of these vessels. There is much variation in the liver tissue adjacent to the thrombi; some of the parenchymal cells are normal, while others show vacuolation or shrinkage in different degrees, and the amount of haemopoietic tissue varies. Histological assessment of these changes was not attempted. In four cases in which thrombi were numerous small areas of necrosis were seen, and within these thrombosis was extensive but more diffuse.

When a larger series of livers was examined it was

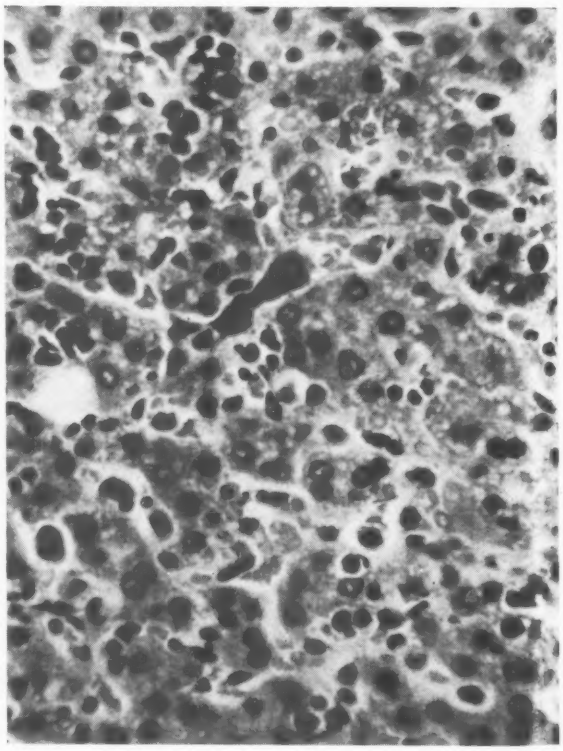

FIG. 1.—A rounded and compact thrombus in a hepatic sinusoid. The baby weighed 1·39 kg. at birth and died at 27 hours with extensive hyaline membrane formation. (Picro-Mallory × 340.)

TABLE 1
THROMBI IN HEPATIC SINUSOIDS: UNSELECTED CASES, 1956-57

	Counts per 50 Fields								
	0	1–4	5–9	10–14	15–19	20–24	25–29	30+	Total
All neonatal deaths	68	38	3	6	10	2	4	5	136
With hyaline membranes ..	3	10	1	5	8	1	4	2	34
Others	65	28	2	1	2	1	0	3	102
Stillbirths	110	12	0	1	0	1	2	5	131

found that thrombi were in fact present in many, although their number varied greatly. In order to separate those cases in which they were absent or few, from those in which they were more numerous, counts were made. Using ×20 objective, thrombi were counted in groups of 50 fields, taking these in line backwards and forwards across the section, and starting where possible at right angles to the serous surface. The thrombi were not counted within areas of necrosis, nor were fields of which necrosis, vessels or portal tracts formed more than half. Between two and eight groups of fields were counted, according to the area of the section, and the means of the counts calculated. The magnification used was the lowest that allowed thrombi to be distinguished from other structures which stained red with the picro-Mallory method.

The investigation was conducted in several steps.

The incidence of thrombi in an unselected group of babies dying in the neonatal period was determined, taking all those examined at autopsy in the years 1956 and 1957 from whom blocks of liver tissue were available. Blocks were of two sorts; the first had been taken at random, while the second, of distinctive shape, had been taken specifically from the right and left lobes. At this stage the random blocks were used, or, if these were not available, those from the right and left lobes were taken together; possible differences between the lobes were considered separately. Livers from stillbirths were also examined; this series was selected in that liver tissue had been processed only from the unmacerated, so that it was confined to babies dying at or shortly before birth. As this part of the survey appeared to establish further the association with hyaline membranes, but did not provide a sufficiently large number of livers to form a suitable control series, additional cases from the preceding three years 1953-55 both with and without hyaline membranes, were selected for examination. Finally, to determine whether similar thrombi occurred more widely in the body, sections of spleen, kidney and adrenal, were examined from those cases in which, in the liver, they were numerous.

Results

Thrombi in Unselected Neonatal Deaths. Sections were examined from 139 livers, but three were excluded because they contained pyaemic abscesses with much surrounding diffuse thrombosis. The counts from the remaining 136 are presented in Table 1.

In 68 (50%) no thrombi were found and in 38 (28%) they were few in number, usually one or two and never more than five per 50 fields; in 27 there were 10 or more per 50 fields. In the further analysis of these results cases with counts of 10 or more are compared with those having less; the former are referred to as 'positive' and the latter as 'negative' cases.

The number of thrombi in babies with and without primary hyaline membranes is compared in the histogram (Fig. 2). This comparison suggests that there is indeed an association between hyaline membrane formation and an increase in the number of thrombi, and of the 27 positive cases no fewer than 20 also had membranes. The two groups, however, those with and those without hyaline membranes, cannot be directly compared; most of the babies with hyaline membranes were premature and had died within a short time of birth, while in the remaining cases there was a much wider range of birth weight and survival. In general, because of such differences, comparison of a group of babies having hyaline membranes with the remaining cases from the same autopsy series will cause confusion by drawing attention not only to those factors related to hyaline membrane formation, but to those related independently to prematurity or to early death. This can be avoided by using a control series matched with the hyaline membrane series by age and maturity. In the group examined in this part of the investigation few cases could be matched in this way, and it was necessary to examine additional ones to form the control series defined in the next section.

Before these results are presented it is of interest to note certain groups in which an increase in the number of thrombi might be expected, but which were in fact 'negative'. First, there were 10 cases in which subcapsular haemorrhage was noted in the liver at autopsy, two of these having in addition small lacerations and a third small areas of necrosis. Second, exchange transfusion through the umbilical vein had been performed on 14 of the 17 babies with haemolytic disease; in one baby who had no fewer than five exchanges, no thrombi were found.

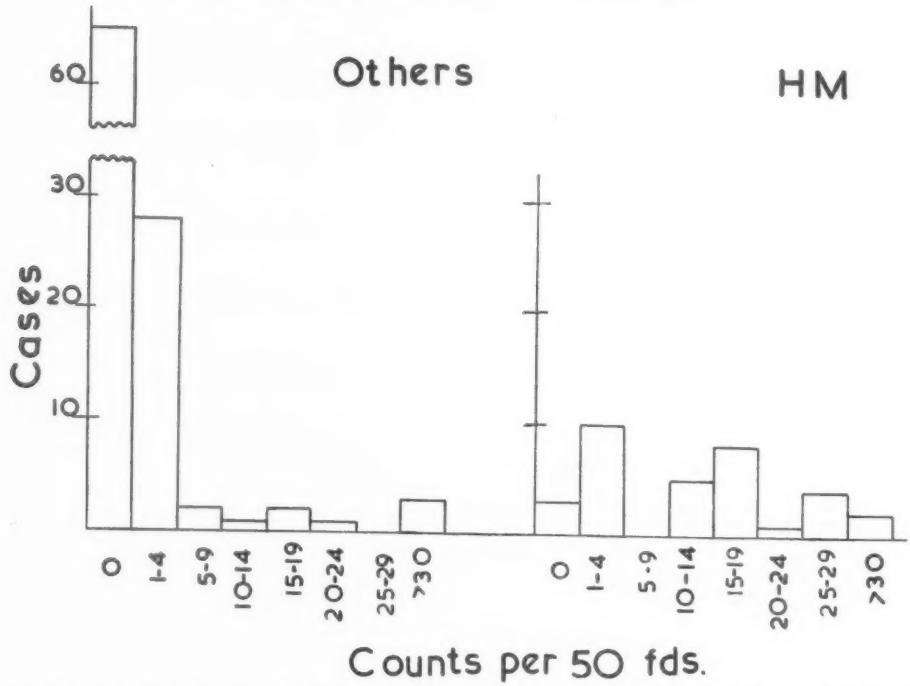

FIG. 2.—Counts of liver thrombi in cases with hyaline membranes (right) and others (left) from the unselected series examined.

Of the 131 fresh stillbirths examined (Table 1) 110 (84%) showed no thrombi, and only nine cases (6·9%) were 'positive'.

Hyaline Membranes and Matched Control Series, 1953-57. The range of the investigation was extended by including further livers from babies dying with hyaline membranes in the years 1953-55; in the whole five-year period blocks of liver were examined from 70 such cases. Most babies with hyaline membranes are premature by the accepted convention of birth weight, and relatively few die who survive for 48 hours; of the 70 cases, 62 were both premature by birth weight and had lived more than one but less than 48 hours after birth. A control series of the same range of birth weight and age was selected from the cases already examined, with additional cases from the years 1953-55; babies with gross congenital malformations were excluded, but otherwise all from whom blocks were available were examined. There were 60 such controls.

The counts from all the cases with hyaline membranes, and from the matched series, are presented in Table 2 and Fig. 3. The increased incidence of 'positive' cases among the babies with hyaline membranes is statistically highly significant (Table 3).

There were, however, 11 'positive' controls and a search was made for factors common to them and the positive cases with hyaline membranes. Two types of lesion appeared on first examination to merit further investigation (Table 4). First, the incidence of intracranial lesions among the positive controls was high, for three had intraventricular haemorrhage, one tentorial tearing with subdural haemorrhage, and one haemorrhage into the falx; in addition, of the four positive cases from the unselected 1956-57 group not included among these premature controls, two had kernikterus, one a tentorial tear, and one was an iniencephalic. Second,

TABLE 2
THROMBI IN HEPATIC SINUSOIDS: MATCHED CONTROL AND HYALINE MEMBRANE SERIES

	Counts per 50 Fields								
	0	1–4	5–9	10–14	15–19	20–24	25–30	30+	Total
Premature controls	31	17	1	3	1	2	1	4	60
Matched hyaline membranes ..	14	15	2	10	9	3	4	5	62
All cases with hyaline membranes	15	17	2	13	10	3	5	5	70

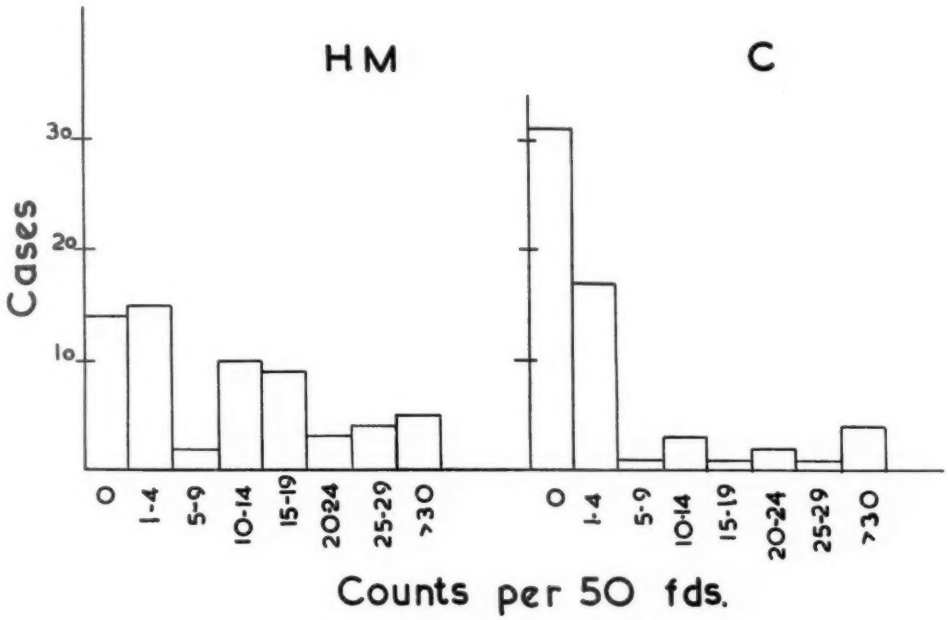

FIG. 3.—Counts of liver thrombi in premature babies living less than 48 hours with hyaline membranes (left) and in matched controls (right).

pneumonia was found in five cases, including two with intracranial lesions, one with renal agenesis, and two who had no other major lesion. The remaining three cases showed only the pleural or pericardial haemorrhages of anoxia, with pulmonary immaturity or atelectasis. However, the distribution of intracranial lesions and of pneumonia among positive and negative cases in both the control series and the hyaline membrane series did not

TABLE 3
MATCHED SERIES

	Positive	Negative	Total
Premature controls	11	49	60
Matched hyaline membranes ..	31	31	62
	42	80	122

$\chi^2 = 13{\cdot}88$
$p < 0{\cdot}001$

TABLE 4
THROMBI IN HEPATIC SINUSOIDS: POSITIVE CONTROL CASES

Case No.	Sex	Birth Weight (kg.)	Crown–Heel Length (cm.)	Gestation (wks)	Age (hrs)	Remarks
Premature Controls						
1	F	2·09	49	41	24	Petechiae of pericardium
2	M	0·94	34	27	5	Intraventricular haemorrhage; pneumonia
3	F	0·86	36	32	24	Petechiae of pericardium
4	M	0·76	36	—	28	Petechiae of pericardium
5	M	1·3	39	29	6	Intraventricular haemorrhage; pneumonia
6	M	1·32	40	30	36	Tentorial tear and haemorrhage
7	F	1·13	39	41	24	Petechiae of pleura and pericardium
8	M	1·52	41	35	5	Renal agenesis; pneumonia
9	M	1·02	37	28	8½	Haemorrhage into falx; pneumonia
10	F	0·73	33	30	12	Pneumonia
11	F	0·66	31	26	5	Intraventricular haemorrhage
Other						
1.	F	1·78	—	37	5 days	Iniencephaly
1.	M	2·6	46	35	3 days	Kernikterus (familial acholuric jaundice)
1.	M	3·26	53	43	17	Tentorial tear and haemorrhage
1.	M	2·74	50	36	53	Kernikterus; haemolytic disease

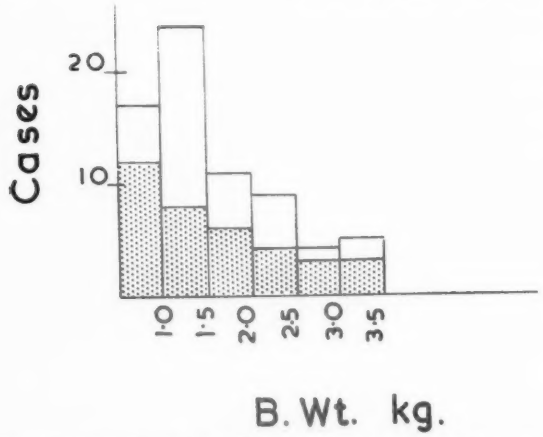

FIG. 4.—The distribution by birth weight of 70 babies with pulmonary hyaline membranes, in 0·5 kg. groups. The 'positive' cases are shaded.

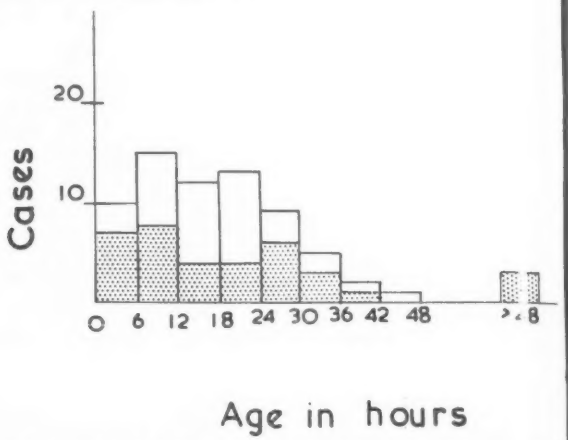

FIG. 5.—The distribution by age of 70 babies with pulmonary hyaline membranes, in six-hour groups. The 'positive' cases are shaded.

suggest that either of these lesions was significantly associated with the formation of thrombi.

An unsuccessful attempt was made to find differences between the 'positive' and 'negative' hyaline membrane cases. Significant differences were not found on examination of their distribution by birth weight (Fig. 4) or by age (Fig. 5), nor when the hyaline membranes were graded histologically for their extent or stage of formation. The incidence of other factors, including the method of delivery, the maternal age or parity, and a history of complications such as pre-eclampsia, antepartum haemorrhage or multiple pregnancy, did not differ between the two groups.

Distribution of Thrombi in Right and Left Lobes of Liver. In recent years attention has been drawn to changes in the liver which reflect either the peculiar pattern of its circulation in the foetus or the alterations in circulation after birth. The vascular supply of the two lobes differs in the foetus. Oxygenated blood returns from the placenta by way of the umbilical vein and, while in part it passes directly to the inferior vena cava by way of the ductus venosus, much of it circulates through the liver; the arrangement of veins is such that the left lobe receives a greater share of this enriched blood. At birth the umbilical vein is obliterated and the ductus closes, probably at once; the difference between the two lobes is then no greater than in the adult. Two consequences of these phenomena have been reported: first, in stillbirths and in some neonatal deaths degenerative changes caused by intrauterine anoxia are more marked in the right lobe (Gruenwald, 1949), and, second, after birth there is a rapid involution of the left lobe with loss of weight, cellular shrinkage and, at certain periods, a greater content of fat (Emery, 1952; 1953; 1956; Emery and Finch, 1954).

As this change of circulation might be thought to cause the formation of thrombi, or to influence their distribution, the cases in which separate blocks had been taken from the right and left lobes of the liver were examined further. Altogether, there were 30 pairs of blocks from the 'positive' cases, 24 of which had hyaline membranes, and 22 from the 'negative' cases. In none of the negative cases did study of the two further sections show a larger number of thrombi on either side. Mean counts for the two sides in the positive cases are presented in Fig. 6; in only two is there a marked preponderance in the left lobe. Comparison of the difference of the means in individual cases did not show a significant increase on either side. While the number of cases examined was small the results did not suggest that this component of the circulatory change at birth had an important influence on the formation of thrombi.

Other Observations. The possibility that the presence of thrombi is not confined to the liver but is more general, was also considered. To examine this, blocks of the spleens, adrenals, kidneys and lungs, from the first 40 positive cases, were recut and stained by the picro-Mallory method. A widespread incidence of capillary or sinusoidal thrombi was not found. In the 40 kidneys examined, no thrombi were seen in the cortices, and single thrombi in the outer medullae of four; a single small thrombus was found in the pulp of one of the 38 spleens; one of the 34 adrenals had a few thrombi within an area of necrosis in the cortex; capillary thrombi

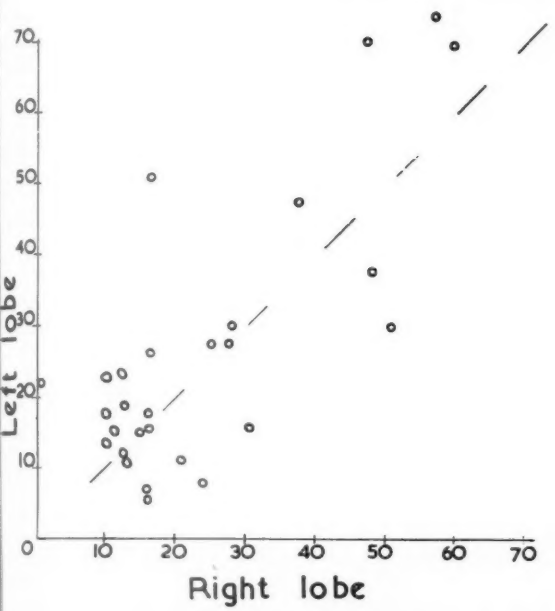

FIG. 6.—Comparison of counts of liver thrombi from the right and left lobes of 'positive' cases.

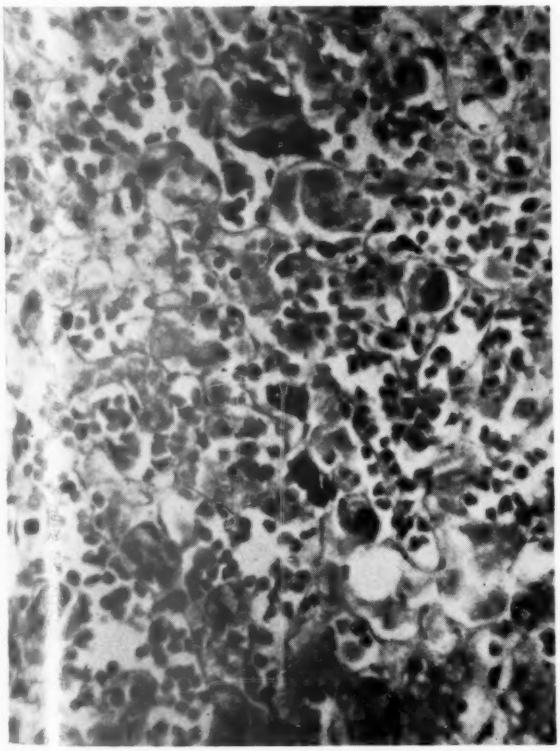

FIG. 7.—Sinusoidal thrombi in the liver of an adult with chronic venous congestion due to cor pulmonale. (Picro-Mallory ×420.)

were found in three of the 40 lungs, with larger thrombi in small arteries of four others. It was concluded that among the organs examined thrombi were numerous only in the liver.

To find out if thrombi were formed in the hepatic sinusoids of older patients, sections from 246 adult autopsies were examined after staining by the picro-Mallory method. The cases were not selected, being roughly consecutive. The histological changes found are summarized in Table 5. Thrombi similar in form to those seen in the newborn were found in only 20 cases, including 14 of the 24 with chronic venous congestion (Fig. 7), five of the 11 with focal necrosis, and one of the 18 with severe fatty change. In most of the livers thrombi were few in number; they were numerous only in four cases with chronic venous congestion, and in these some recent necrosis in the central parts of the lobule was also seen. In the cases with chronic congestion the thrombi usually lay in the central atrophic zone, but were sometimes seen outside this between apparently normal parenchymal cells; where there was focal necrosis the thrombi were found between the necrotic cells, and, as in the newborn, the thrombosis was occasionally more diffuse.

TABLE 5

THROMBI IN HEPATIC SINUSOIDS OF ADULTS

Lesions in Liver	Total	Thrombi Present
Chronic venous congestion	24	14
Focal or centrilobular necrosis	11	5
Fatty change	18	1
Cirrhosis	14	0
Secondary carcinoma	11	0
Reticulosis	14	0
Pyaemic abscesses	2	0
Amyloid	1	0
Miliary tuberculosis	1	0
None	150	0
	246	20

These observations are of interest, for they give an indication of the circumstances under which sinusoidal thrombi may form. In all cases but one there had been circulatory disturbance, either prolonged, as in chronic venous congestion, or more acute, as in the cases with focal necrosis in which cell death was caused by anoxia at sites determined by local reduction in blood flow. The occurrence of thrombi in larger numbers in cases of heart failure only where there is recent necrosis suggests that their formation is probably less the result of the chronic congestion than of a later exacerbation of failure with further decrease in cardiac output.

Discussion

Several explanations of the genesis of the lesions found in the livers of the newborn are possible, but certain of these may be readily discounted. First, these are true thrombi and have not formed after death; although a cellular reaction to them has not been seen, their rounded and compact form suggests exposure to the blood flow during life and contrasts with the regular pattern of fibrin strands seen in post-mortem clot; their distribution in the body is not general. Second, the possibility of their being embolic must be considered. There are three routes by which emboli could reach the liver, the umbilical and portal veins, and the hepatic artery. Those carried by the hepatic artery should, however, be more widely distributed, at least to those organs supplied by the descending aorta. There is nothing to suggest the constant presence of any lesion in the field of drainage of the portal vein in these cases. Emboli could be carried through the umbilical vein only before birth, when they would be expected to be found more frequently in stillborn infants, to be found in larger numbers in the left lobe of the liver and also to pass into the general circulation by way of the ductus venosus and the foramen ovale. The distribution of thrombus formed by the action of any agent carried in the blood should be similar; it has been suggested (Boyd, 1958) that certain of the small thrombi seen in the lungs of newborn babies are, like those seen in women dying after amniotic fluid embolism, formed by the action of thrombogenic substances from the placenta.

The hypothesis most in accord with the observations made is that the thrombi form in the site in which they are seen, in the baby as in the adult, as a result of a disturbance of circulation leading to its local reduction with consequent anoxia, a process which when severe may cause in addition focal necrosis. This is of interest, for it now seems likely that pulmonary hyaline membranes arise by the compaction of fibrin-containing oedema fluid and that a disorder of circulation contributes, in the newborn as in certain older patients, to membrane formation. The importance of the occurrence of large numbers of thrombi in babies with hyaline membranes thus lies in their providing further evidence of the presence of a circulatory disturbance in such cases.

Summary

The presence of small thrombi in the hepatic sinusoids of the newborn is described, and their incidence is shown to be significantly higher in babies with pulmonary hyaline membranes. In the series of adult livers examined similar thrombi are found, with one exception, only where there is chronic venous congestion or focal necrosis, and it is suggested that in the newborn their increase indicates a disturbance of circulation.

My thanks are due to Professor A. C. P. Campbell for his advice on the preparation of this paper, to Professor W. I. C. Morris in whose department the work reported was performed, and to Dr. F. A. Langley for allowing me access to the autopsy material. Some of the observations are presented in a thesis accepted for the degree of Doctor of Medicine by the University of London.

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PULMONARY HYALINE MEMBRANES, ASPIRATION AND PNEUMONIA

BY

T. WADE-EVANS

From the Departments of Pathology and Obstetrics, University of Manchester

(RECEIVED FOR PUBLICATION AUGUST 25, 1960)

The structures now called hyaline membranes were first described in the lungs of the newborn baby by Hoccheim (1903), and were considered by him to be aspirated vernix caseosa. At present there is little evidence that hyaline membranes arise as a direct result of aspiration, although aspirated substances may be included within them; many conflicting views of their pathogenesis have been held, but opinion is now in favour of their origin within the lung itself, from material, probably protein, lost through the local capillaries. Until fibrin was identified within the membranes the exact mechanism by which they developed remained uncertain, for it was difficult to understand how they could be formed from soluble serum proteins, unless these were in the process grossly denatured. A rational explanation of the formation of membranes became possible, however, after the demonstration with fluorescent antibody of their fibrin content (Gitlin and Craig, 1956); further studies using orthodox histological methods confirmed the observations of these workers and showed that the membranes arose as a result of incomplete resorption of fibrin-containing oedema fluid, and suggested that fibrin was indeed their essential component.

An important conclusion drawn from this finding is that the membranes found in the lungs of newborn babies do not differ structurally from those of older patients, in whom membranes may form in a variety of diseases. In all of these there is a temporary increase in capillary permeability which is great enough to allow the escape of fibrinogen as well as of other plasma proteins; the conditions include not only inflammatory lesions and neoplastic or other infiltrations of the lung itself, but also cardiovascular disturbances, in particular severe left ventricular failure, with or without uraemia. Membrane formation in these cases is merely one common end result of a number of different pathological processes, and the possibility that this may be so in the lung of the newborn must be considered. In older children and adults membrane formation sometimes complicates pneumonia (Farber and Wilson, 1932). In the newborn these two processes are often found together; the relation between the two conditions is often, however, difficult to determine. Before the past decade hyaline membranes in the newborn were most frequently discussed in papers concerned primarily with pneumonia; although at that time origin of the membranes from vernix was generally accepted, Steinharter (1937) recognized structures in the newborn which he considered to differ from 'vernix membranes' and to be the result of pneumonia. Potter (1952) believed pneumonia was an important complication in many babies with hyaline membranes, particularly in those who died after the end of the second day. More recently the concept of the membranes forming as the result of a specific pathological process or 'hyaline membrane disease' has been widely held, so that less attention has been paid to the possibility of their origin in other ways.

In this paper cases are presented in which membrane formation in the lungs of the newborn is secondary to pneumonia, and an attempt is made to define histological criteria for the recognition of such membranes; the observations recorded show that in about one-fifth of all cases in which membranes are present they are the result of an inflammatory process. The membranes found in other babies, in whom their origin is independent of pneumonia, are, to distinguish them, referred to as 'primary' hyaline membranes.

Material

During the 10 years 1949-1958 autopsies were performed at St. Mary's Hospitals, Manchester, on 800 babies dying in the neonatal period, histological material being available from 791; of these, 727 (91·9%) died in the first week of life. The cases described below were discovered during a review of sections taken from the lungs of these babies, and they include many in which diagnosis was difficult. Membranous structures were found in

175 of the lungs, 143 being of the type defined above as 'primary'. The remaining 32 cases are discussed in this report; they are presented in three groups in the order in which my attention was drawn to them.

Group I: Hyaline Membranes and Aspiration

In this group membranes are seen where there has been gross soiling of the lung by aspirated material. Epithelial squames from the liquor amnii are seen in the lungs of many of the babies who die *in utero* or soon after birth; when present in small numbers these are probably without significance, but when numerous they are usually held to indicate prenatal anoxia, showing an increased aspiration of amniotic fluid as a result of increased intrauterine respiratory movements. The squames seen in these circumstances are separate, dispersed and readily drawn into the finest air spaces, although they may there become concentrated and packed into small groups by the absorption of amniotic fluid. Sometimes, however, squames are present in a more coarsely particulate material, e.g. meconium, vernix caseosa or mucus from the respiratory tract, and this may plug bronchi or bronchioles, causing atelectasis or obstructive emphysema (Emery, 1956). In the series reviewed, widespread aspiration of such material had occurred in 25 cases, and in six of these there were also eosinophil membranes; their presence recalls the original theory of formation of hyaline membranes from vernix caseosa, and might in the past have been held to support it. The existence of structures of this type was recognized by Gruenwald (1953, 1958) who suggested that hyaline membranes might be of different sorts and that true 'vernix membranes' were found in a small number of more mature babies.

The first case is typical of the group.

Case 1. A 23-year-old primigravid patient, 43 weeks pregnant, was delivered by caesarean section because of foetal distress; eight hours after the onset of labour the membranes ruptured spontaneously with drainage of heavily meconium-stained fluid, and foetal bradycardia was noted. The baby (birth weight: 2·85 kg.; crown-heel length: 55 cm.) was asphyxiated at birth, but after meconium had been removed from the respiratory tract began at three minutes to breath regularly. Slight cyanosis persisted, however, with occasional apnoeic attacks, the baby's condition deteriorating shortly before death at 36 hours. At autopsy, the significant findings were in the respiratory system; the lungs were expanded and heavy (right: 58 g., left: 46 g.; heart: 25 g.), with irregular areas of aeration alternating with wedge-shaped areas of dull red-purple colour in all lobes. The bronchi contained dark green mucoid material.

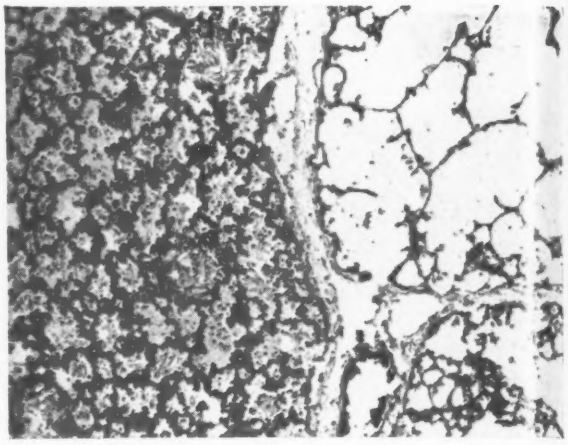

FIG. 1.—Case 1: the variation in pattern between adjacent aerated and unaerated lobules is seen. (H. and E. × 48.)

On histological examination, there was a striking variation in pattern between neighbouring secondary lobules (Fig. 1). Many were aerated; some indeed were overdistended; others were not, but retained the pattern of the foetal lung, the lumina of the air spaces being either narrow or slightly distended, containing fluid in which there were moderate numbers of polymorphonuclear leucocytes mixed intimately with squames. The lungs appeared mature; there was little mesenchyme between the terminal air spaces and, while individual cuboidal lining cells persisted, they were not numerous; the form and distribution of the surviving cuboidal cells was identical in both aerated and non-aerated lobules. Many small bronchi and bronchioles were obstructed by a mixture of wisps of mucus and clusters of anucleate squames; a few rounded masses of mucus with a little granular yellow pigment were also present.

Eosinophil membranes were seen in a number of the unaerated lobules (Fig. 2), but not elsewhere. They

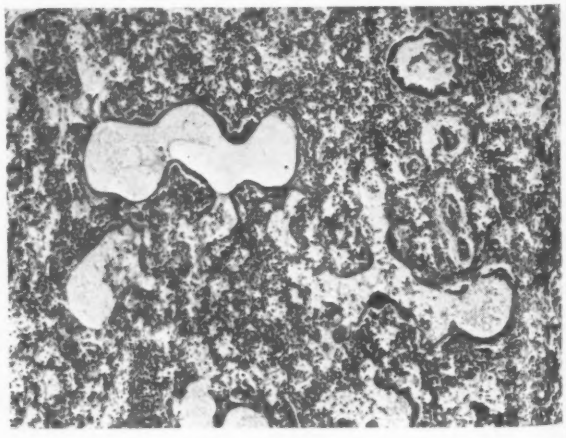

FIG. 2.—Case 1: examples of the membranous structures seen in some of the unaerated lobules. (H. and E. × 48.)

FIG. 3.—Case 1: eosinophil material identical with that forming the membranes lies in close association with the aspirated material, but is proximal to it. (H. and E. × 96.)

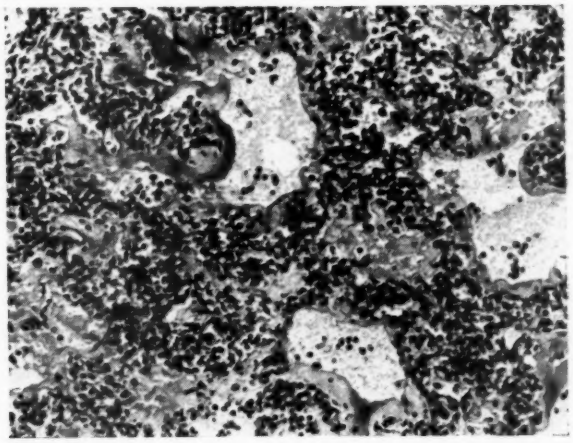

FIG. 4.—Case 1: the membranes are continuous with exudate seen in the more peripheral air-spaces. (H. and E. × 130.)

were usually thick and formed a complete lining for the enclosing air space, often extending into the terminal bronchioles. In places they lay close to masses of aspirated material and were proximal to it (Fig. 3). This association was not constant, however; indeed, the membranes were seen only in those areas in which there was pneumonia, and in places appeared to be in direct continuity with the exudate (Fig. 4). Strands of eosinophil material were sometimes seen adjacent to the meconium blocking the bronchi, but only where there were also leucocytes. The membranes themselves contained small numbers of polymorphs that were well preserved, their appearance contrasting with that of the pyknotic or fragmented round nuclei sometimes seen in primary hyaline membranes. The exudate was in general of the diffuse type seen in congenital or intrapartum pneumonia, although there were also a few foci of more recent origin, which lay proximal to the membranes and which contained larger numbers of polymorphs with many coarse strands of fibrin; these strands were haematoxyphil and also gave the Feulgen reaction. In some places oedema fluid had collected proximal to the membranes and contained small numbers of polymorphs.

Comment

The gross and microscopical appearances of the lungs in the other cases of this group were similar and the features of all six are summarized in Table 1. It will be noted that in five meconium was found at autopsy in the bronchi or had contaminated the amniotic fluid. In all of them the lungs showed alternating masses of bright pink aerated and of dull red-purple airless tissue which appeared to be secondary lobules as they were wedge-shaped and were separated on the pleural surfaces and in the sub-pleural regions by connective tissue septa. In five this pattern of alteration was seen throughout, while in the sixth aeration was confined to the right upper lobe. The aerated lobules often appeared overdistended, as if there had been incomplete obstruction of the supplying bronchioles; three cases were complicated by interstitial emphysema, one of them with pneumothorax.

The membranes in these cases differed in several ways from those commonly seen in premature infants with respiratory distress. Their distribution was patchy, rather than widespread and even throughout the lungs; they occurred in babies who, where the air passages were not obstructed, were able to expand and aerate their lungs normally; the lungs were not immature and the pattern attributed to 'resorption collapse' (Potter, 1952) was not seen. Certain differences in structure have been emphasized in the description of Case 1; the membranes where present were usually thick, formed a complete lining for the air-spaces in which they lay, and not infrequently extended to line the terminal bronchioles; they often contained apparently healthy leucocytes, rather than the pyknotic or fragmented epithelial nuclei included in primary hyaline membranes.

While the occurrence of membranes in these cases suggested that the eosinophil as well as the particulate material had been aspirated, this was not so. Membranes or similar eosinophil material were found only where there was an inflammatory reaction, in some fields lying in continuity with the exudate; they were found in none of the 19 other cases examined in which there was widespread aspiration of mucus or meconium with little accompanying pneumonia; it seemed obvious that they were formed by the action of respiration on such exudate, either by the initial expansion of the containing

lung at birth, or by the continued pressure of inspired air after this time.

The nature of the pneumonia was less certain. It was apparently not due to the chemical irritation of the aspirated substances, for these could lie in the lung without reaction, in some cases for nearly two days, in parts adjacent to those in which there was exudation and membrane formation. It was more likely to be the result of infection, although no organisms were seen in the sections, and culture was negative in the two cases in which it was attempted: these babies had, however, been given antibiotics. Estimation of the time at which infection occurred was difficult. In places the exudate was similar in character to that seen in the 'congenital' pneumonia of infants who are stillborn or who die soon after birth; in these the terminal air spaces are slightly distended, usually regularly and with preservation of the 'crumpled' pattern of the unaerated foetal lung, and the exudate contains small or moderate numbers of leucocytes mixed intimately with squames or scraps of mucus, with but little detectable fibrin. It is less easy to interpret this type of reaction in babies who survive for longer times, although when it is found in those dying at any time in the first day it can be assumed that the pneumonia in these cases too has arisen before birth. In the group of cases under discussion assessment was made difficult by the survival of most into the second day, and by the presence in many of fresh focal pneumonia. Aspiration must, however, have occurred during labour, or at the latest soon after birth, and the close association of the exudate with the aspirated material suggested that the pneumonia had commenced at the same time, and that at least in some of the cases it was of intrapartum origin.

Group II: Membrane Formation in Diffuse Pneumonia

To investigate this further, a search was made for membrane formation in babies who had died within a few days of birth, and whose lungs showed diffuse pneumonia without evidence of aspiration, other than that of the commonly seen dispersed squames; in addition, a series of lungs containing hyaline membranes was reviewed for the presence of diffuse pneumonia. Eighteen cases of membrane formation in diffuse pneumonia were found, and

TABLE 1

DETAILS OF CASES IN GROUP I

Case	Sex	Birth Weight (kg.)	Crown-heel Length (cm.)	Maturity (wks)	Age (hrs)	Maternal		Other Features
						Age (yrs)	Parity*	
1	M	2·89	55	43	36	23	1	Caesarean section for foetal distress; liquor meconium stained; regular respiration established at 3 minutes, but later apnoeic attacks *Autopsy:* lungs aerated but heavy with dull red-purple wedge-shaped areas; green mucoid material in bronchi
2	M	2·78	50	40	31	23	1	Pregnancy and early labour normal; vertex delivery with cord wound around neck; baby gasped intermittently for 45 minutes before regular respiration commenced *Autopsy:* lungs heavy (Rt. 46 g., Lt. 53 g.) and similar in appearance to those of Case 1; small tentorial tear
3	M	3·03	53	42	18	37	1	Admitted after rupture of membranes, draining meconium-stained liquor; normal vertex delivery 12 hours later; much meconium aspirated from air-passages *Autopsy:* lungs showed a similar pattern with, in addition, interstitial emphysema (Rt. 45 g., Lt. 37 g.)
4	F	2·72	53	42	32	32	1	Normal labour with vertex delivery; baby breathed at once, but much mucus removed from air passages; remained cyanosed with rapid respiratory rate *Autopsy:* interstitial emphysema of lungs and mediastinum without pneumothorax; bronchi contained meconium; alternating areas of aeration and 'atelectasis'
5	F	2·82	52	42	12	19	1	Short normal labour; membranes ruptured a little before birth; liquor heavily meconium stained; respiration began soon after birth, but was rapid and grunting *Autopsy:* interstitial emphysema with left pneumothorax; alternating areas of aeration and 'collapse' noted; left tentorial tear
6	F	3·60	55	40	38	25	2	Short normal labour; much meconium removed from respiratory tract; respiration rapid with persistent cyanosis *Autopsy:* lungs heavy and dull purple throughout (Rt. 40 g., Lt. 32 g.) with aeration of right upper lobe only

* After the birth of the baby examined.

TABLE 2
DETAILS OF CASES IN GROUP II

Case	Sex	Birth Weight (kg.)	Crown-heel Length (cm.)	Maturity (wks)	Age (hrs)	Maternal		Other Features
						Age (yrs)	Parity*	
7	M	2·07	48	42	12	23	3	Medical induction two weeks after expected date of delivery; short normal labour with late rupture of membranes *Autopsy:* lungs heavy (Rt. 30 g., Lt. 22 g.), uniformly deep purple and unaerated; no other significant finding
8	M	2·75	48	32	9	30	5	Maternal mitral stenosis; membranes ruptured spontaneously five days before onset of labour *Autopsy:* tentorial tear and subdural haemorrhage; lungs similar to above (Rt. 33 g., Lt. 28 g.)
9	M	1·75	43	32	12	—	2	Spontaneous premature labour; district delivery; other details unknown *Autopsy:* lungs heavy and airless (Rt. 27 g., Lt. 22 g.); no other significant finding
10	M	0·85	33	27	2	33	4	Spontaneous onset of premature labour three days after membranes had ruptured; normal vertex delivery *Autopsy:* 'atelectasis' (Rt. lung 11 g., Lt. 9 g.)
11	F	1·51	42	32	25	36	1	Surgical induction of labour using Queen Charlotte's Hospital bag three days before delivery; maternal pre-eclamptic toxaemia; vertex delivery *Autopsy:* intraventricular haemorrhage extending into subarachnoid space; lungs heavy and airless (Rt. 20 g., Lt. 16 g.)
12	M	1·30	38	28	1	25	1	Leaking amniotic fluid for six weeks before delivery; fluid bloodstained for three days; pre-eclamptic toxaemia; breech delivery *Autopsy:* subarachnoid haemorrhage; lungs heavy (Rt. 31 g., Lt. 24 g.)
13	M	2·45	50	36	5·5	25	1	Surgical induction of labour for pre-eclampsia, by artificial rupture of membranes; normal vertex delivery 52 hours later; breathed soon after birth but severe apnoeic attack at 1 hour *Autopsy:* lungs 'atelectatic' (Rt. 12 g., Lt. 10 g.); no other important finding
14	M	0·75	33	26	4	35	1	Twin pregnancy: first twin; spontaneous rupture of membranes two days before onset of labour; breech delivery *Autopsy:* tentorial tear and subdural haemorrhage; lungs 'atelectatic' (Rt. 10 g., Lt. 9 g.)
15	F	1·13	38	32	8	28		Twin pregnancy: second twin; membranes ruptured for seven days; breech delivery; first twin stillborn *Autopsy:* 'atelectasis' (Rt. 12 g., Lt. 10 g.)
16	M	3·7	55	40	12	23	4	Membranes ruptured spontaneously 38 hours before onset of labour; normal vertex delivery; regular respirations after seven minutes, but cyanosed with rib retraction; later apnoeic attacks *Autopsy:* haemorrhage into left cerebral hemisphere; lungs appeared aerated (Rt. 36 g., Lt. 31 g.)
17	F	1·81	44	32	3	19	2	Spontaneous premature rupture of membranes two days before normal delivery; irregular respiration from birth with apnoeic attacks *Autopsy:* lungs showed infrequent areas of aeration (Rt. 32 g., Lt. 25 g.); no other significant findings
18	F	1·44	41	33	7	23	2	Born before arrival; vertex delivery, but other details unknown *Autopsy:* bilateral tentorial tears with subdural haemorrhage; lungs airless (Rt. 12 g., Lt. 9 g.)
19	F	0·93	37	28	9	26	2	Spontaneous onset of premature labour; vertex delivery after late rupture of membranes; baby gasped at birth but respiration not established for nine minutes *Autopsy:* intraventricular haemorrhage; lungs airless (Rt. 20 g., Lt. 15 g.)
20	F	1·67	32	39	31·5	25	2	Paracentesis amnii five days before normal vertex delivery; haemolytic disease; exchange transfusion not performed *Autopsy:* lungs expanded but not aerated (Rt. 32 g., Lt. 22 g.)
21	F	3·51	51	37	6	29	7	Spontaneous onset of labour with late rupture of membranes; paracentesis amnii had been performed six weeks before; haemolytic disease; vertex delivery; exchange transfusion begun at one hour; collapsed and died at 6 hours *Autopsy:* haemoperitoneum; lungs airless (Rt. 27 g., Lt. 22 g.)

TABLE 2 (*continued*)

Case	Sex	Birth Weight (kg.)	Crown-heel length (cm.)	Maturity (wks)	Age (hrs)	Maternal		Other Features
						Age (yrs)	Parity*	
22	M	1·26	38	32	36	22	3	Spontaneous rupture of membranes five days before delivery; vertex delivery; cried well at birth and breathed regularly; sudden collapse at 33 hours *Autopsy:* lungs dull purple and airless (Rt. 18 g., Lt. 14 g.); no other significant finding
23	M	1·81	43	32	13	26	4	Spontaneous onset of labour with late rupture of membranes; haemolytic disease with severe anaemia; given digoxin and exchange transfusion attempted, but collapsed and died *Autopsy:* lungs airless, with a little fibrinous exudate on pleura (Rt. 29 g., Lt. 23 g.)
24	F	2·0	43	37	24	24	1	Membranes ruptured before admission with pre-eclamptic toxaemia; forceps delivery 39 hours later; baby cried well after birth but had cyanotic attacks at 1½ and 4½ hours, then persistent cyanosis *Autopsy:* intraventricular and subarachnoid haemorrhage; lungs dull purple and airless (Rt. 25 g., Lt. 20 g.)

* After the birth of the baby examined.

their pathological features are illustrated by the following examples. The histories and post-mortem findings are summarized in Table 2.

Case 7. A 23-year-old woman had previously had two normal deliveries at term. In her third pregnancy labour was induced medically at 43 weeks; it started promptly and was of short duration, with the normal vertex delivery of a male child. The membranes were intact until the beginning of the second stage (Stage I: two hours 10 minutes; II: 15 minutes; III: 10 minutes). The baby weighed 2·07 kg., being thus by the accepted convention premature, but it was of wizened appearance, and seemed in other ways mature; the crown-heel length was 48 cm. and ossification centres were present in the lower femoral epiphysis and talus. Observations on the placenta were unfortunately not recorded, but the mother was neither toxaemic nor hypertensive. At autopsy, the lungs were expanded, but not aerated, were dark in colour and relatively heavy (right: 30 g., left: 23 g.; heart, 17 g.). No other lesions of importance were found.

On histological examination, in spite of the low birth weight, the lungs appeared mature. There was little aeration although here and there the terminal bronchioles, with the spaces immediately beyond them, were rounded, some appearing empty and others containing oedema fluid (Fig. 5). The more distal air spaces, while retaining the foetal pattern, were regularly expanded, and they contained moderate numbers of polymorphonuclear leucocytes, which were mixed with amniotic squames and surrounded by granular eosinophil material; in this it was not possible to demonstrate fibrin. Diffuse haemorrhage had occurred into a few lobules. In places there was denser exudate with coarse strands or masses of fibrin, some of which showed an ill-defined patchy basophilia and gave the Feulgen reaction. Membranous structures were seen in much of the tissue, but their distribution was not regular. Some were eosinophil and of fibrillary or granular

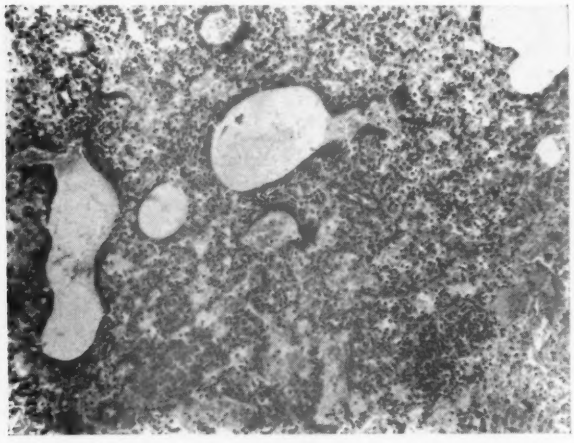

FIG. 5.—Case 7: membranous structures in a lung with diffuse pneumonia. (H. and E. × 69.)

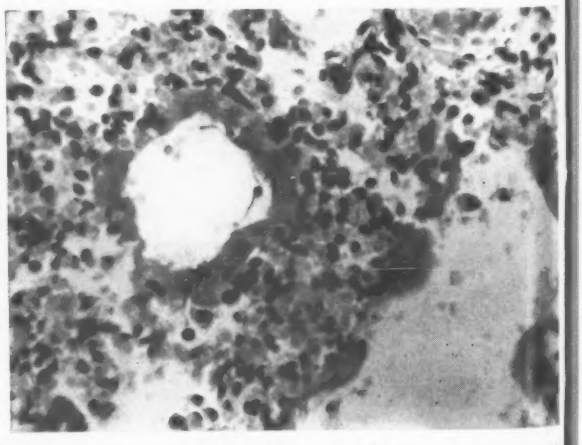

FIG. 6.—Case 7: eosinophil membranes which more closely resemble the 'primary' hyaline membranes seen in babies with respiratory distress. (H. and E. × 254.)

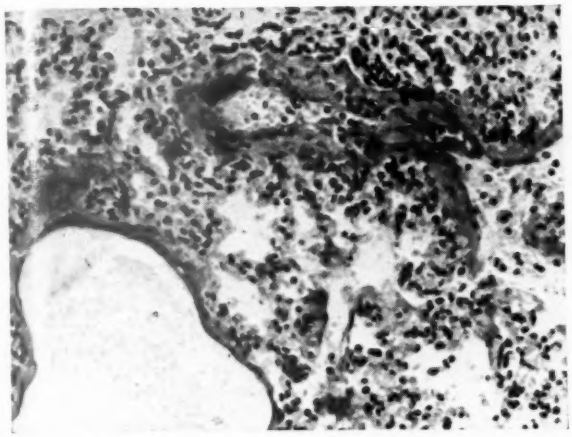

FIG. 7.—Case 7: some of the membranes (left) have ill-defined basophil areas which resemble those seen in the exudate (upper right). (H. and E. × 158.)

texture, without other feature, and as such were identical with primary hyaline membranes (Fig. 6). Others were less well formed, being of open texture with ill-defined surface; they were often incomplete or ragged, forming masses on the free margins of the alveolar or saccular septa, as if the lung tissue peripheral to them had been expanded since their formation. In a few places the membranes were thicker, more complete and similar in structure to the dense exudate described above, with ill-defined basophilia and Feulgen staining (Fig. 7).

Case 8. Labour started in a 30-year-old woman five days after spontaneous premature rupture of the membranes. She had mitral stenosis, but had previously had three normal deliveries at term without ill effect. Labour was short (Stage I: two hours 50 minutes; II: 10 minutes; III: 15 minutes), with normal delivery of a male child. Although the maturity given by the mother's history was 32 weeks, he weighed 2·77 kg. and the crown-heel length was 48 cm.; the siblings had weighed between 3·0 and 3·5 kg. at term. The baby was slow to breath and had apnoeic attacks at 2½ and 7 hours, with a third, from which he did not recover. at 9 hours. Autopsy showed a right tentorial tear with subdural haemorrhage; the lungs were expanded and heavy, but not obviously aerated (right, 33 g., left 28 g.; heart 17 g.).

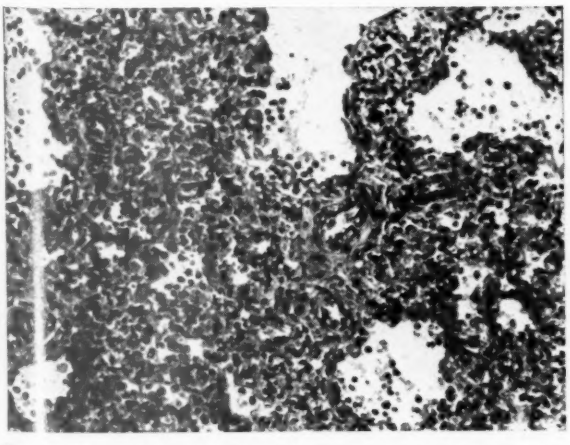

FIG. 8.—Case 8: ragged eosinophil membranes forming in a lung with diffuse pneumonia. (H. and E. × 137.)

On histological examination, the lungs appeared less mature than in the previous case, although the birth weight was greater. Here, too, the pattern was uniform, without aeration, other than of occasional bronchioles or alveolar ducts, but with regular expansion of the distal spaces, which contained polymorphs and squames, and, in places, denser exudate similar in character to that seen in Case 7. Membrane formation was patchy, being commonest where pneumonia was most marked; some membranes showed the staining reactions of the exudate and others were more uniformly eosinophil, if with ragged surface (Fig. 8).

Comment

The assessment of diffuse pneumonia of this type is not easy; it most commonly arises *in utero* as the result of aspiration of infected liquor amnii, although to distinguish between the presence in the lung of such fluid and an inflammatory reaction to it is often difficult. The importance of the pneumonia is uncertain, although it is probably not often the sole cause of death; it is usually of low grade, so that it may not harm an unhandicapped baby, being often seen at autopsy either in those who have suffered intrauterine anoxia, or in those who have died as the result of separate more severe lesions, and who presumably would have survived the infection alone. The difficulty of estimating the time at which this type of pneumonia begins has been discussed already; in the cases in this group it seems likely that the process had begun intrapartum, for all but three died in the first day, some within a few hours of birth, the lungs remaining for the greater part of foetal pattern, and the distribution of the exudate being characteristically diffuse.

In cases with such pneumonia, as was shown by Langley and Smith (1959) in stillbirths and neonatal deaths taken from the same autopsy series as was drawn on here, there was an increased incidence of inflammation of the foetal surface of the placenta, and of prolonged rupture of the membranes before delivery. It is of interest to note that in nine of the 16 cases in which adequate details of the obstetric history were available there was prolonged rupture of the membranes, and that in three others there had been recent surgical interference with the uterus, in two surgical induction of labour two and

a half days before, and in the other paracentesis amnii five days before birth.

The membranes in these cases were often difficult to distinguish from primary hyaline membranes, and at times the two might indeed appear identical. Differentiation can often be made on the structural features of the pneumonic membranes, and by their patchy distribution; while the causative pneumonia is diffuse, it shows irregular accentuations, and the membranes are seen where these are most marked. There may be ill-defined basophil areas of the type illustrated, a feature rare in the absence of inflammation. The membranes may be laminated and may, like those seen in Group I, line the bronchioles as well as the respiratory part of the lung. Their ragged or incomplete appearance contrasts with that of fully-formed primary hyaline membranes, as does the expansion of the lung tissue distal to them.

However, it may not always be possible to make this distinction. If the inflammatory reaction in an intrapartum pneumonia continues when respiration is established after birth, with further exudation, the process becomes identical with that by which primary hyaline membranes are formed from fibrin escaping through the pulmonary capillaries; in the latter, also, small numbers of polymorphs may be present. In addition, primary hyaline membrane formation may be complicated by pneumonia, and, while this is often focal and intense, there is sometimes a more diffuse spread, both central to the membranes and, if the air spaces are not completely collapsed, peripheral. Nevertheless, the two processes remain essentially separate, and it is important to distinguish between them wherever possible.

Group III: Miscellaneous

Membranous structures were seen in a further eight cases. In a number they were of sparse distribution, were poorly formed, or occurred in babies who had survived for several days and in whom extensive fresh pneumonia made interpretation difficult. Two are of interest in that membranes were formed in the course of a pneumonia obviously acquired after birth; the changes, illustrated in the case presented below, recall those described by Farber and Wilson (1932) in older children with streptococcal lobular pneumonia.

Case 25. Premature labour began spontaneously in a negress, para 10, and a female child was born who cried well soon after birth. The maturity seemed greater than that given by the mother's history (28 weeks; weight 1·63 kg.; crown-heel length 43 cm.). At the end of the second day respiratory distress was noted,

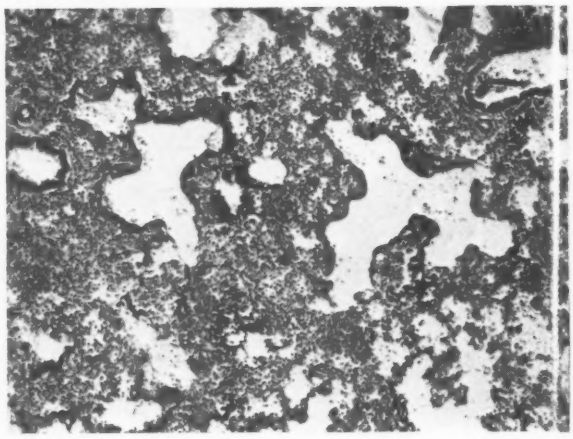

FIG. 9.—Case 25: membrane formation in acquired pneumococcal pneumonia. (Picro-Mallory × 48.)

and in spite of treatment the child died at 58 hours. At autopsy, there were areas of consolidation and haemorrhage in the right lower and middle lobes with surrounding oedema, although elsewhere the lungs were aerated.

Histological examination of the consolidated areas showed dense inflammatory exudate, with large numbers of polymorphonuclear leucocytes, coarse strands of fibrin, and haemorrhage. Many diplococci were present, some intracellular, and these were gram and P.A.S. positive; culture gave a pure heavy growth of *Streptococcus pneumoniae*. No aspirated material was seen. Brightly eosinophil membranes (Figs. 9 and 10) were seen lining the alveolar ducts at the margins of the larger areas of consolidation and throughout the smaller ones, but were not found elsewhere. The membranes, unlike most of those in Group I and II stained strongly as fibrin with phosphotungstic-acid haematoxylin and the picro-Mallory method. In the other lobes the tissue was aerated.

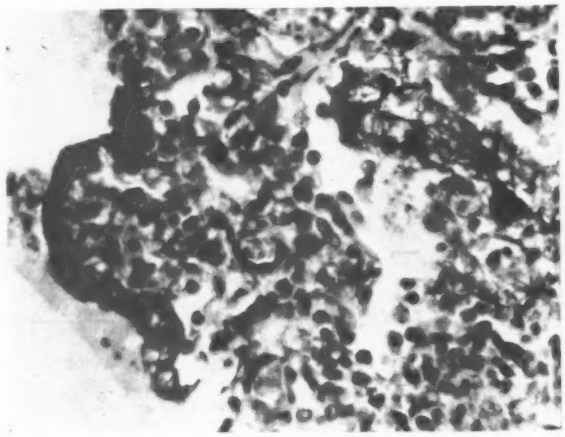

FIG. 10.—Case 25: the membranes stain strongly as fibrin and contain coarse strands resembling those seen in the exudate (right). (Picro-Mallory × 254.)

Discussion

The formation of membranes in the course of pneumonia of newborn babies has been described. In one group of cases the inflammation was localized and associated with aspiration of meconium or similar material, in another it was diffuse, without evidence of such aspiration, but presumably also of prenatal origin, and in a third it was acquired after birth. The membranes can usually be differentiated by their structure from the hyaline membranes that occur with respiratory distress, although this is not always possible; in the absence of such structural features their uneven distribution and association with inflammation may allow distinction to be made. As in other respiratory diseases of the newborn it is important to examine adequate samples of lung tissue.

Information about the babies in Groups I and II is given in the Tables. It will be noted that over one-third of the babies in Groups I and II were mature, by the accepted convention of birth weight. Primary hyaline membranes are uncommon in such babies, unless there is maternal diabetes mellitus and this was not the case here. Also, in Group II most deaths occurred in the first day, and in a number in the first few hours after birth, when formed primary hyaline membranes are rare; it is possible that some of the cases dying within one to two hours of birth and reported as having hyaline membranes are of this type, and that this is the explanation of the rare cases, such as that recorded by Morison (1952), in which membranes are seen in stillbirths after attempted resuscitation. Most babies with primary hyaline membranes die within two days after birth, and those that survive longer usually die as a result of complications; it is likely that the fresh membranes seen in babies of greater age arise during an acquired pneumonia, and that some of these are the result, as may be similar structures in the adult, of the aspiration of irritant material such as gastric content. A pneumonic pathogenesis should be considered whenever primary hyaline membranes are diagnosed, particularly in the lungs of mature babies, of those dying within a few hours of birth, or of those surviving for more than two or three days.

These membranes are merely incidental formations in the course of an inflammatory reaction in the lungs, and it is not likely that they cause in themselves any additional disturbance of respiratory function; the importance indeed lies in their possible confusion with primary hyaline membranes. The significance of the latter is still uncertain, although a fuller understanding of their origin would contribute greatly to our knowledge of the changes occurring at birth in both the respiratory and cardiovascular systems; and it is important to exclude cases with pneumonic membranes from the further statistical or other investigations of this problem.

Summary

The hyaline membranes found in the lungs of newborn babies have been shown to consist essentially of fibrin, so that they do not differ in their nature from those found in older patients. In the latter membranes may arise in the course of a number of different pathological processes, and the possibility that this is so in the newborn is considered. Cases are presented in which membranes have formed in the lungs of the newborn as a result of pneumonia, in one group with accompanying aspiration of meconium or other material, in a second without evidence of aspiration but also intrapartum in origin, and in a third acquired after birth. The importance of such membranes lies in the possibility of their confusion with 'primary' hyaline membranes that arise in association with respiratory distress, particularly in mature babies, in those who have died within two or three hours of birth, or those who have survived for more than two days after birth.

My thanks are due to Professor A. C. P. Campbell for his advice on the preparation of this paper, to Professor W. I. C. Morris in whose department the work reported was performed, and to Dr. F. A. Langley for allowing me access to the post-mortem material. Some of the observations are presented in a thesis accepted for the degree of Doctor of Medicine by the University of London.

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THE AGE AT MENARCHE IN ASSAM AND BURMA

BY

C. V. FOLL

From the Burma Oil Co. (1954) Ltd., Rangoon

(RECEIVED FOR PUBLICATION AUGUST 17, 1960)

Most of the reports from India on the age at menarche have been based on recollected ages of commencement of the periods and the accuracy of these is doubtful. Examples of such ages vary from 13·42 years (Israel, 1959) based on replies from 2,227 women from different parts of India to 14·88 years (Shah, 1958) based on questionnaire forms completed by 2,391 Hindu girl entrants to Gujarati University, Ahmedabad, in West Central India. Two other series are quoted by Shah from the same area of India—989 girls of Maharaja Sayajirao University during 1950, 1951 and 1952, had an average recollected age at menarche of 13·8 years, and during 1954, 2,370 girls in high schools in Poona had an average recollected age at menarche of 14·06 years.

The technique adopted in this study was to ask the girls their age and whether or not they had started menstruating. From the data obtained (Tables 1 and 2) the average age of onset of menstruation was calculated by the statistical technique of probit analysis. In Assam this average age was found to be 13·21 $\pm$ 0·11. In a study in Burma by Foll (1958) a menarcheal age of 14·40 was reported; unfortunately the calculation was in error, and the corrected value is 13·25 $\pm$ 0·08. In both these series the probit technique gave an excellent fit to the data. The standard deviation in Assam was 1·62 years and in Burma 1·12 years.

The 1,150 girls in the Digboi, Assam, series were mostly Assamese, Bengalis and Nepalis with a few Central and Southern Indians, and the majority came from Hindu families, although there were some Buddhists, Sikhs, Christians and Muslims. In the Chauk, Burma series, the 702 girls were predominantly Burmese Buddhists, with a few Chinese, Indians or Anglo-Indians. If the method of probit analysis is to be used with success it is essential that the girls being interviewed should have an accurate knowledge of their ages, and ages in the tropics are notoriously unreliable. It is only in communities where accurate birth dates are required for making personal horoscopes (e.g. in Burma where Birth Notices in the Press often include the exact time, to the nearest second, of the birth) or where there is a settled community having adequate birth records, e.g. in some missions or amongst an industrial company's employees that any accuracy may be expected.

Studies by probit analysis have been reported by Wilson and Sutherland (1953), and include a series by Ellis (1950) in Southern Nigeria (Thomson 1952), and their own work in Nigeria, Ceylon and England. Their results are summarized in Table 3 and compared with the Assamese and Burmese findings.

TABLE 1

NUMBER OF GIRLS AND AGE AT MENARCHE IN DIGBOI, UPPER ASSAM

Age (years)	Numbers Having First Menstrual Loss		Total
	Yes	No	
8	0	181	181
9	3	207	210
10	3	193	196
11	11	167	178
12	39	101	140
13	45	65	110
14	45	18	63
15	37	6	43
16	22	1	23
17	6	0	6
Total ..			1,150

TABLE 2

NUMBER OF GIRLS AND AGE AT MENARCHE IN CHAUK, UPPER BURMA

Age (years)	Numbers Having First Menstrual Loss		Total
	Yes	No	
10	0	72	72
11	1	91	92
12	8	85	93
13	49	58	107
14	71	20	91
15	100	3	103
16	74	1	75
17	47	2	49
18	20	0	20
Total ..			704

TABLE 3

AGE AT MENARCHE IN NIGERIA, CENTRAL INDIA, CEYLON, BURMA AND ASSAM, COMPARED WITH SOUTHERN ENGLAND*

Series	No. of Children	Age at Menarche	
		Mean Age (years)	Standard Deviation (years)
Southern Nigeria (Ellis, 1950):			
Ibo and Yoruba, Series 2	142	14·40	Not available
Northern Nigeria (Wilson and Sutherland, 1953):			
Plateau Pagans	74	14·50	1·24
Northern girls at school	172	14·14	0·61
Central India (Thomson, 1952):			
Aboriginals, Munda, Oraon, Santal	411	14·65	1·55
Ceylon (Wilson and Sutherland, 1950a):			
Rural Cingalese	296	14·39	1·73
Colombo City schools: Various Eastern races	844	12·84	1·24
Burma:			
Mostly Burmese	702	13·25	1·12
Assam:			
Mostly Assamese, Bengalis and Nepalis	1,150	13·21	1·62
Southern England (Wilson and Sutherland, 1950b)	2,590	13·49	1·19

* All data obtained from probits.

Factors that may Influence the Age at Menarche

Most girls start menstruating between the ages of 9 and 18, and outside these wide limits, puberty may be considered precocious or delayed, the cause being either over-activity or lack of activity of one or more members of the endocrine system. For the purpose of this report these two groups of cases may be ignored.

The factors to be considered here as affecting the age at menarche are race, climate, nutrition and socio-economic position.

Race. In the past, it was stated frequently that Jewish girls started menstruating early and Eskimo girls late. The truth of the latter has been questioned by Levine's (1953) finding that the age at menarche of Alaskan Eskimo girls was 14·4 years. Ito (1942) showed that in Los Angeles there were significant differences in the age at menarche of American, European, Japanese, Negro and Chinese girls at the same college. However, even this study may not be free from nutritional or socio-economic conditions. Ellis (1950) has written: 'Heredity, . . . whilst it may affect the age of puberty of the individual, is probably not of major importance when communities of different ethnic stock living under similar social and environmental conditions are compared.' However, in India it is difficult to find different ethnic stocks living in the same place under similar social conditions, and this study throws little light on this aspect of the problem.

Climate. The data for Table 3 were obtained from places in the world which had considerable variation in their climates. Lagos, lying about 450 miles north of the Equator in Southern Nigeria, has an average annual rainfall of 72 in. and a humid atmosphere with temperatures rising to 90° F. On the other hand, the Northern Nigerian Savannah is hot and dry, and the plateau temperate. In the Assam-Burma series, Chauk, a town of some 25,000 inhabitants, is situated in the 'dry zone' of Burma almost 1,500 miles north of the Equator, and has an average rainfall of 24 in. with temperatures rising to 112° F. In contrast, Digboi, a town of about 60,000 inhabitants in Upper Assam, and approximately 450 miles due north of Chauk, has an average rainfall of 120 in. with temperatures in the wet summer months rising to over 100° F. Thus the two groups of girls (of different races) lived under vastly different climatic conditions, although their socio-economic conditions were similar and the basic item of diet, rice, was the same. The ages at menarche were 13·21 (Assam) and 13·25 (Burma). Similarly, in Nigeria, where again there were considerable climatic differences, the ages at menarche were 14·40 (Southern) and 14·14 (Northern).

It is suggested that the effect of climate has been unduly stressed in the past. The pendulum of opinion has swung back from the view that children mature earlier in the tropics, and possibly overswung to the view of Mills (1937) who states 'sexual maturity in tropical countries comes fully two years later than in most stimulating temperate regions'. Wilson and Sutherland (1953) write: 'It is, however, clear that in tropical countries the onset of menstruation is not determined solely by the climate'. In spite of animal experiments in which it was shown that a hot moist atmosphere may retard sexual maturity (Ogle, 1934), it is considered doubt-

ful whether, in fact, climate plays any part in affecting the age at the onset of the menses.

Nutrition and Socio-economic Position. It is impossible to discuss nutrition adequately without reference to the socio-economic position of the girls because the latter largely determines the former. The girls in this series, both in Assam and Burma, were daughters of oil company employees and must be considered as economically better placed than the average in either country. Ellis (1950) writes that 'Since school children in Nigeria represent a privileged section of the community, it may be assumed that the nutrition of those included in the survey would be above the average of children in the southern provinces generally, where probably less than 20% of girls of school-age are in fact attending school'. The evidence for stating that higher socio-economic groups mature earlier has been detailed by Tanner (1955). In her All-India survey, Israel (1959) found that girls from the higher income groups were younger at menarche than those from less well-to-do homes.

Nutrition is probably the most important of the many causes for this socio-economic difference. Ellis (1950) has described the Southern Nigerian diet as being largely vegetable (yams, cassava, cornflour, plantains, etc.) with little meat and no milk, but with some fish. The Burmese diet is based on rice, with vegetables and occasionally meat curry. Fish is plentiful in Chauk since it lies on the east bank of the Irrawaddy and is usually used as a soft tasteful paste (Ngapi) in preparing the Burmese curry and soup (hingyo) or as 'Balachaung' a mixture of Ngapi, dried prawns and chillies. Both these preparations provide a valuable additional source of protein. Cow and buffalo milk is seldom given to children. The great majority of children in Burma are well nourished and food taboos are rare (Foll, 1959), as contrasted with the protein cultural blocks of Bengal (Jelliffe, 1957). In Assam, there are modifications in the diet due to the different ethnic groups. On the average, weaning takes place later than in Burma and nutritional deficiencies in children are commoner. The basic items of the diet are dhal (legume) and rice, the latter being of a much poorer quality than in Burma and often considerably adulterated with dirt, stones, etc. Milk, also adulterated, is drunk by children, but green vegetables and vegetable broths are seldom eaten.

In neither place is malaria a problem, never occurring in Chauk and now very rare in Digboi. The incidence of intestinal infestation (particularly ascaris) was appreciably higher in Digboi than in Chauk.

It would be of considerable interest to carry out regular surveys of the age at menarche in the so-called socially undeveloped countries and note whether any change in age occurs with social development.

Summary

The age at menarche in Assam calculated by probit analysis is 13·21 ± 0·11 with a standard deviation of 1·62 and in Burma is 13·25 ± 0·08 with a standard deviation of 1·12 (the latter figure being a correction to a previous study).

The two groups of girls were from a privileged section of the community.

Of the factors that may influence the age at menarche it is submitted that climate plays no part, race but little, and that socio-economic circumstances and nutrition are most important.

I am most grateful to Dr. Tanner, of the Department of Growth and Development, Institute of Child Health, London, for his help and encouragement, and also for the care with which he and Mr. Howard Simpson of the Department of Statistics, Rothamsted Experimental Station, Harpenden, have checked my attempts at statistical calculation.

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Erratum

In a study in Burma by Foll (1958), a menarcheal age of 14·40 years was reported; the calculation was in error and the corrected value is 13·25±0·08.

AN ANALYSIS OF ADMISSIONS TO THE PAEDIATRIC DIVISION, MULAGO HOSPITAL IN 1959

BY

LATIMER K. MUSOKE

From the Paediatric Division, Mulago Hospital, Kampala, Uganda

(RECEIVED FOR PUBLICATION SEPTEMBER 1, 1960)

The last review of admissions to the Children's Ward at Mulago Hospital was for the year 1950-51 by Davies (1954) and, as in all rapidly developing countries the pattern of childhood disease seemed to be varying considerably in response to numerous ecological changes, it was felt that a further more recent study of admissions would be valuable.

Ecological Background

During the past decade, there has been a large influx of population into Kampala and the adjacent Mengo District of Buganda, and, in addition, people are becoming more and more hospital conscious. Both changes have considerably increased the number of attendances at hospital, thereby creating special problems in looking after an increasing number of patients without an expanding bed space.

An index of the size of the problem is suggested by the fact that, while Uganda's total population is six and a half millions (1960 census), 44% of these are children. Kampala and Mengo District have shown the greatest increase in population of all parts of Uganda.

The majority of our patients are the Baganda living in rural areas. The parents are peasant farmers, and the cultivation is done by the husband and wife or wives, assisted by labourers for those who can afford to engage them, using a hoe as the only implement for cultivation. There are no villages, but scattered homes; the way of life and the type of houses are changing rapidly. The demand for this change has focused the energies of most people on growing cash crops. Those who can read and write and speak some English drift to the towns to seek jobs in the expanding commercial town of Kampala.

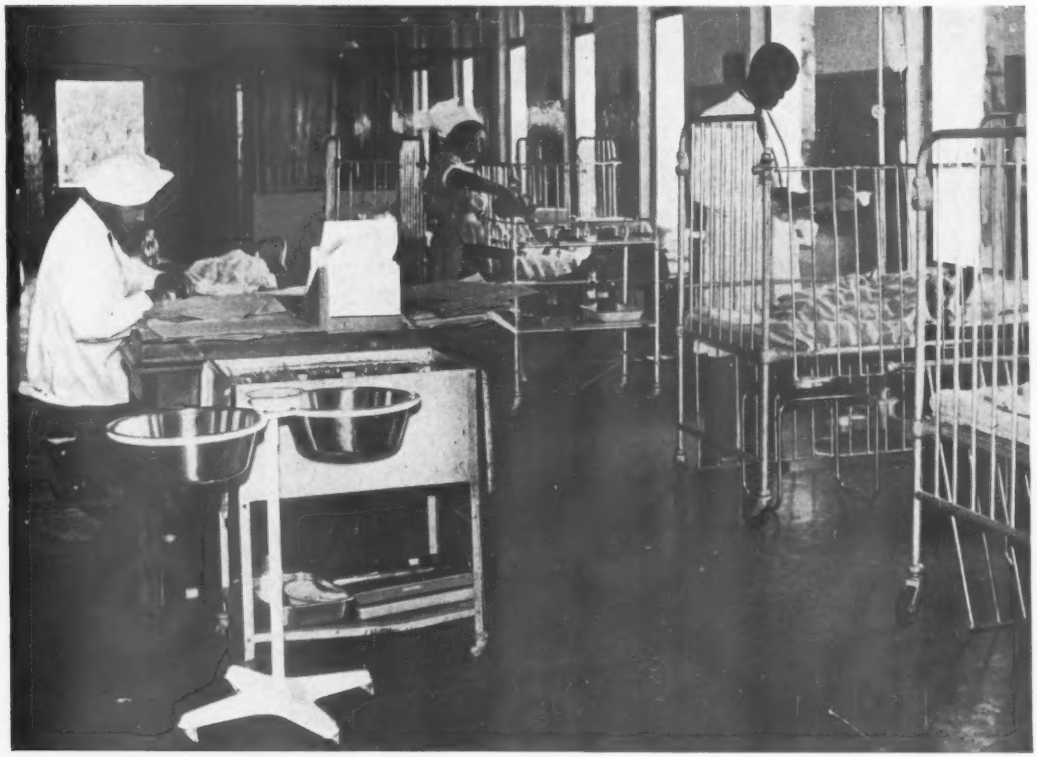
The life of the mothers of most of our patients is very arduous. She has the responsibility of growing food for the family, assisting the husband in cultivating fields of cash crops, providing water and firewood for the family and looking after her own four to eight children. Means of transport are difficult, although getting easier in most parts of the country. It is with these problems that the mother has to forsake her home and other children to bring her sick infant to hospital. This is reflected in the late arrival of many of the cases admitted and the high mortality soon after admission.

The life of the educated and wealthier people is easier. They have quick means of transport. Mothers can attend child welfare clinics around Kampala, can afford to add milk to their children's diet and take their children sooner for medical advice.

The immigrant tribes, designated as 'others' in this paper, include the Luo, Toro, Kiga, Nkole, Nubians, Lugbara, Nyoro, Alur, Lango, Atesot and Acholi, some of whom live in scattered housing estates around the town, and the overcrowded built-up slum areas that are found around big towns all over East Africa. They live the double life of working in towns until they have saved enough money to go home and stay at home for months before returning to work. They may or may not have their families with them. Their social problems are similar to those of other rapidly expanding towns in East Africa.

The other big single group of immigrant tribes is that of people from Ruanda-Urundi, who come to work on large non-African plantations or get employed in rural areas on African farms. They face the strain of the journey, meet the problem of shortage of food in a subsistence agricultural community, work and save money to take home, and are exposed to new and different kinds of tropical parasites, as, for example, the severe manifestations of clinical malaria seen in those arriving in Kampala from the mountainous non-malarial parts of Ruanda-Urundi. A higher incidence of kwashiorkor is found in children of this group.

The Paediatric Division is part of Mulago Hospital, the teaching hospital of the University College



of East Africa. In-patient facilities consist of 50 beds with daily admission of cases from the children's out-patients and cases seen after hours in the casualty department.* There is no 24-hour laboratory service. An attempt is made to carry out certain simple routine examinations on all admissions and, in fact, they are done in about 85% of cases. These include blood slides for malarial parasites, wet film preparations for sickling, haemoglobin estimations and stool examinations, which are carried out in a ward side room by a technician whose services are available from 8 a.m. to 4 p.m. on weekdays. Special blood investigations can be sent to the hospital haematologist and the biochemical laboratory. Tests are done by the Government biochemists, working in a laboratory a mile away from the hospital. It is under such circumstances of daily admissions, without laboratory assistance after 4 p.m., in an overcrowded ward (see Fig.), that the care of children, 81% of whom are below 3 years of age, has to be accomplished.

* The number of children attending the hospital, however, is so large that the present beds of the Paediatric Division are sufficient in number to cope only with the children up to the age of about 6 years. Older children are accommodated in adult wards and are not included in this review. Also omitted are a number of children admitted to the T.B. ward, ophthalmic and to surgical wards for specialist's care. This situation should be partly rectified when the New Mulago Hospital is opened.

Admissions

This analysis covers admissions to the Paediatric Division during the year 1959. The total number in the ward register was 1,380.

The overall grouping of causes of admission has been classified according to their order of frequency and their mortality (Table 1).

Diseases have been classified as separate entries according to the main diagnosis on admission; therefore, each case appears once in the Table, although a combination of diseases in the same patient was a very common finding.

The turnover of patients in the ward is very high. Many patients die soon after admission, before any investigations are done. Autopsies are very often refused. It is in the light of these difficulties that the diagnoses have to be interpreted.

The preponderance of males over females is observed and cannot be explained as the census figures for this country give the ratio between males and females as about equal.

Gastro-intestinal Diseases. Out of 231 cases admitted in this group, 200 were suffering from gastro-enteritis, 38 (18%) of whom died. Other conditions were: six enteric fever (all recovered); 10 intestinal obstruction (five intussusception, three

TABLE 1

Disease	Sex		Deaths		% Mortality in Each Group	Total
	Male	Female	Male	Female		
Gastro-intestinal	133	98	24	22	15	231
Malnutrition	105	78	28	8	20	183
Malaria	104	77	11	13	13	181
Respiratory	114	66	15	17	17	180
Anaemia	77	73	8	11	13	150
Tuberculosis	43	30	9	5	19	73
Miscellaneous	131	100	39	32	30	231

ileus from infection, one impacted faeces, one with no cause found after laparotomy), with four deaths; 12 liver disease (classified as: six infective hepatitis, four cirrhosis of the liver and two undiagnosed hepatic disease); three cases of liver disease died. All the helminthic diseases have not been included in this group as they would rarely be causes for admission, although three cases of clinical disease due to ascariasis were admitted, with one death from peritonitis, without perforation, being found at autopsy. Hookworm disease, a severe and common malady, has been considered separately.

Malnutrition. In this group, kwashiorkor, with 136 cases, makes up 10% of the admissions, with the highest mortality of 20%. The marasmus group is made up for the most part of cases of failure to thrive as a result of inability to manage artificial feeding, combined with intercurrent infections. There were 47 cases, approximately 4% of admissions, with six deaths.

Malaria. All cases with positive blood slides for malaria are not included here; it is only the cases where clinical malaria was the main reason for admission that are considered. In 26 cases (out of the total of 181), the diagnosis was only clinical without a positive blood slide for malaria.

Respiratory Diseases. Out of 180 cases, pneumonia was diagnosed in 113 children, with 23 (20%) deaths. Twenty-nine were suffering from laryngo-tracheo-bronchitis, with seven (24%) deaths; eight with bronchitis (one death) and four with pertussis (one death). Other conditions seen were: acute upper respiratory infections 23, bronchial asthma two and pulmonary collapse one. All recovered.

Anaemia. Of the total admissions, 144 cases (10·4%) were classified as anaemia; 61 cases were admitted due to hookworm anaemia, with five (8·3%) fatal results. The diagnosis of sickle cell anaemia, made in 66 children, was based on positive sickling, dactylitis, characteristic radiological bony changes and presence of haemoglobin S on electrophoresis (the latter being necessary as 17% of healthy Baganda have the sickle cell trait). In 17 cases, the anaemia was of uncertain origin.

Tuberculosis. Of the total admissions 73 (5·3%) were suffering from tuberculosis, i.e. pulmonary 60, with a mortality of 18%; bone four, with one fatal case; meningitis five, with two deaths, and glandular four, all recovering.

Miscellaneous. Other causes for admission, that are not mentioned above, will be analysed later.

Age and Sex

Some of the mothers can give a reliable age and sometimes the exact date of birth of their children in the first two years. In the case of illiterate parents, who can only recall the age from memory, it is considered that the accuracy is fair for infants, but in the older children ages can only be roughly expressed.

The grouping of the ages in years for all admissions is shown in Table 2.

It can be seen that the childhood morbidity is greatest in the first two years of life and steadily decreases thereafter. This is also shown in Table 3, which gives the incidence of the various major disease groups at different ages.

TABLE 2

Sex	Age Groups (years)							
	0–1	1–2	2–3	3–4	4–5	5–6	6+	Not Recorded
Male	308	214	105	49	48	20	23	15
Female	230	146	77	30	27	17	30	9
Total ..	538	360	182	79	75	37	53	24

TABLE 3
INCIDENCE OF VARIOUS MAJOR DISEASE GROUPS AT DIFFERENT AGES

Disease	Age							
	6 mths	6 mths–1 yr	1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	6+ years
Gastroenteritis	18	108	50	12	8	1	2	2
Kwashiorkor	—	20	80	27	5	3	1	1
Marasmus	20	11	13	3	—	—	—	—
Malaria	25	46	67	26	8	7	2	—
Respiratory diseases	46	40	52	25	3	5	6	1
Hookworm anaemia	2	6	14	23	7	5	5	1
Tuberculosis	3	24	22	7	4	7	4	2

Neonatal Disease. Eighty-three newborn babies were admitted to the ward, with the diseases shown in Table 4.

TABLE 4
83 NEONATAL ADMISSIONS TO GENERAL PAEDIATRIC WARD

Disease	Number	Deaths
Gastroenteritis	11	6
Pneumonias	11	5
Congenital abnormalities	11	3
Tetanus neonatorum	10	10
Prematurity	10	5
Umbilical sepsis	10	4
Feeding problems	7	1
Unexplained neonatal jaundice	6	2
Purulent meningitis	3	3
Birth injury	3	2
Cellulitis of back	1	—

This does not, in fact, necessarily represent the local pattern of neonatal disease as sick newborn babies are also nursed in a side ward adjacent to the maternity ward; while, owing to the very short stay in hospital after delivery (necessitated by the extremely heavy bed pressure in the Maternity Division), it is likely that many neonatal diseases occur after discharge, and the babies may not be brought back for therapy.

Tribal Distribution

The pattern of life for people living in towns is becoming more uniform and the record of a patient's tribe, for those in the same income group, is often more likely to indicate his geographical origin rather than a different way of living. The only tribal distinction which is significant for the people around Kampala is to divide them into those families who produce practically all their vegetable food from their gardens and those who have to buy it from the market. It is generally accepted that the Ruanda-Urundi and other tribes who form the majority of the labourer class in Buganda are at an economic and nutritional disadvantage, and obtain most of their food from markets.

There are two rainy seasons each year and it is only in exceptional circumstances, when the rains fail, that actual shortage of food is experienced in this part of the country. It seems, therefore, that the factors leading to severe malnutrition are not mainly attributable to shortage of food, but to the low protein content of the staple food used in this country and to lack of knowledge of nutritional needs.

The tribal distribution of the admissions was as follows:

Tribes	Male	Female	Total
Ganda	455	378	833
Ruanda-Urundi	120	80	200
Others	200	100	300

The admissions of major disease groups analysed according to tribe are shown in Table 5.

TABLE 5
ADMISSIONS ACCORDING TO THE MAJOR DISEASES, ANALYSED BY TRIBE

	Ganda	Ruanda-Urundi	Others
Gastroenteritis	134	15	51
Kwashiorkor	70	40	21
Marasmus	19	16	10
Malaria	133	13	35
Respiratory diseases	117	22	40
Hookworm anaemia	22	32	7
Tuberculosis	38	18	17

Seasonal Variation

Analysis of total admissions on a monthly basis showed no significant seasonal variation (Table 6.)

TABLE 6

Month	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
Cases	102	101	110	108	114	128	121	100	104	118	121	118

TABLE 7

	Age (years)							
	0–1	1–2	2–3	3–4	4–5	5–6	6	Not Recorded
No. of cases admitted	538	360	182	79	75	37	53	24
No. died	97	68	22	16	6	6	11	16
% deaths/admissions	18	19	12	20	8	16	21	67
% total deaths	40	28	9	7	2	2	5	6

This failure to demonstrate seasonal variation in the admissions does not exclude its existence, but rather suggests that the demand for beds is all the time so much above the available bed space. As no more cases are allowed to the ward than the number of beds admit, the variation in the number of cases requiring admission has to be considerable to cause variation in the figure of admissions each month.

Deaths

The overall distribution of deaths according to age is given in Table 7.

As might be expected, the highest wastage of life is in the first year of life.

In the group where age was not recorded the mortality rate was 67%, which suggests that many died soon after admission before being fully examined. It is not possible to give the exact time to the hour spent in hospital before death, as the time is not recorded when the patient enters the hospital, when he is seen by a doctor or when he arrives in the ward. It is useful, however, to note that 93 patients died within 24 hours of their admission and 28 within the second 24 hours. Of the deaths, therefore, 50% occurred within 48 hours of arriving in the hospital.

Autopsies were performed in only 34 (14%) cases. It is obvious that the problem of obtaining consent for autopsies from parents and relatives is great.

Consideration of Main Disease Groups

(I) Diarrhoea and Vomiting Syndrome (Gastro-enteritis). It is significant that a disease which seven years ago was considered to be quite uncommon, now tops the list of admissions. Davies (1954) stated that diarrhoea and vomiting were relatively unimportant causes for admission of children in Mulago Hospital. Welbourn (1955) noted that the cases of diarrhoea and vomiting in her child welfare clinics were relatively mild and did not require hospital treatment.

The present analysis shows that the diarrhoea and vomiting syndrome has become one of the major problems in the ward. Luder (1956) classified his cases into groups according to the cellular exudate in the stools, severity of diarrhoea and vomiting, and the degree of dehydration. It has not been possible to do the same in the present series, as cases did not form part of a special investigation.

The duration of stay in hospital averaged 4·4 days, and details are given in Table 8.

The age distribution of children with gastro-enteritis is given in Table 9.

It can be seen that the age incidence has its peak under 2 years of age and becomes rarer thereafter, thus behaving like diarrhoea and vomiting in the temperate zones (Luder, 1956).

In the cases with prolonged and severe diarrhoea, potassium deficiency was suspected in a number of cases. This was observed clinically by ileus, hypotonia, cardiac irregularity and localized woody oedema. Lack of adequate biochemical laboratory facilities prevented the estimation of electrolytes in the blood in most cases. Without a 24-hour laboratory service results are not likely to be in time to assist in the immediate treatment of the patient.

TABLE 8

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cases	34	31	33	33	19	10	11	4	4	3	3	—	4	10

TABLE 9

Age (years)	< 6 mths	6 mths	1–2	2–3	3–4	4–5	5–6	6
Cases	7	119	50	12	8	1	1	2
Deaths	25		9	2	—	—	1	1

Similarly, bacteriological investigation was not possible. However, in a series of 100 cases reported previously by Wilson and Luder (1957) pathogens were found in 33 cases (*Shigella* 25, *Salmonella* 6, *Escherichia coli* 3—one child having a double infection).

TRIBE AND DIET. There is a low incidence in the Ruanda-Urundi group (15 cases) and the highest incidence is in the Baganda (134 cases).

Dietary data showed that only 27 children were exclusively breast fed at the time of illness, while 23 were bottle fed only, 68 were breast fed with supplements of cow's milk and 35 were receiving a solid diet. Adequate details were not available in 45 children.

The interpretation of this tribal distribution and method of infant feeding is probably principally related to the fact that in the Ruanda-Urundi breast feeding is not only more universal and prolonged but, more important, is given unsupplemented. In the Baganda, although many do still breast-feed their babies, early supplementary feeding is increasing and, as feeds are often prepared in an unhygienic way, this predisposes to gastroenteritis.

MALARIA. Blood slides were examined for malaria in 156 (78%) cases of gastroenteritis, only nine were recorded positive for malarial parasites and in only three was a heavy parasitaemia recorded. It appears, therefore, that malarial diarrhoea and vomiting has not contributed much to the large number of cases in this series. Parenteral infection is said to cause in the temperate zones 30% (Scott, 1953) to 60% of the cases (Greaves and Welch, 1951, quoted by Luder, 1956). In the present series its status is uncertain, but it was not often considered to be aetiologically significant, although in two cases chronic otitis media was present and in another child, pneumonia was recorded.

ANAEMIA. Haemoglobin estimations in this type of infection are given in Table 10.

DEATHS. Thirty-eight (19%) patients died, 12 (31%) dying within 24 hours of admission. In 31% of the cases, admission was after a seven-day history. Many patients were admitted with a very severe degree of dehydration, not infrequently associated with malnutrition.

(II) Malnutrition. In this series, protein-calorie malnutrition formed 14% of the total admissions and caused the highest mortality. There have been several recent reviews of the subject (Jelliffe, 1959). Welbourn (1955, 1958) has discussed feeding problems, as seen in this country.

In the present series, the following tribal and age distributions were found in kwashiorkor and in marasmus (Table 11).

Whereas in kwashiorkor the highest incidence is between the first and second year of life, in the marasmus group the main incidence is in the first six months of life. The figures here are unreliable as, due to the shortage of bed space, only the severely ill cases were admitted.

ADDED INFECTIONS AND INFESTATIONS

(i) *Malaria.* In 82% of the cases blood slides were examined for malarial parasites; 25% were recorded positive. Davies (1954) recorded 46% cases of kwashiorkor complicated by malaria in the Ganda and non-Ganda together.

(ii) *Hookworm.* In 64% of the cases stools were

TABLE 10

Hb (g./100 ml.)	< 4·2	4·2–5·6	5·6–7	7–8·4	8·4–9·8	9·8–11·2	11·2–12·6	12·6–14
Cases	2	3	12	18	53	39	15	2

TABLE 11

		Age							
		0–6 months	6 mths–1 yr	1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	6 years
Kwashiorkor:									
Cases	Ganda	—	12	43	11	4	1	—	—
	Others	—	8	37	16	1	2	1	1
Deaths	Ganda	—	2	9	—	3			
Marasmus:									
Cases		20	11	13	3	—	—	—	—
Deaths		2	—	4	—	—	—	—	—

TABLE 12

Hb (g./100 ml.) ..	< 4·2	4·2–5·6	5·6–7	7·0–8·4	8·4–9·8	9·8–11·2	11·2–12
Kwashiorkor	13	24	17	20	28	12	1
Marasmus	2	2	6	7	10	3	2

examined and 38% of those examined were recorded as having hookworm ova, but whether it was a light or heavy infection it was impossible to say.

(iii) *Ascaris*. Only three positives were recorded among the 87 stools examined. These figures do not give the true picture of the diseases complicating kwashiorkor, as investigations were not carried out in every case.

(iv) *Respiratory Infections*. These include pulmonary tuberculosis and are known to be common in kwashiorkor. Davies (1954) was of the opinion that they were almost part of the disease. They are known to be as common as before; penicillin administration formed part of the routine treatment.

It can be seen that most of the cases were quite anaemic (Table 12). The nature of the anaemia was not investigated specifically and because of the multiple pathology in many of the cases it was usually difficult to be certain of the aetiology. It is known that, apart from the infections and infestations present, deficiency of protein, iron and folic acid can contribute to the anaemia of kwashiorkor. The marasmus group were not as anaemic as the children with kwashiorkor.

Five children required blood transfusions. In these, the stools were positive for hookworm ova in four out of five, so that the anaemia could be at least partially attributed to these helminths.

The dietetic history was not analysed. The diagnosis of mild forms of malnutrition is very difficult in a country where infection and infestation with worms are very common. A fact which parents of a patient cannot understand is how a child can develop malnutrition in spite of eating and satisfying his hunger with starchy foods, such as steamed plantain (*matoke*). A comparison of the common foods eaten in this country with milk, as regards the protein-calorie ratio, shows that, even if the food eaten can satisfy hunger, it cannot provide the protein required for the growing child. Milk provides 15 to 20% of the calories from proteins; plantains, yams and sweet potatoes provide 3 to 6% of the calories from proteins and cassava about 2%. A child requires 14% of his calories from proteins. It is the understanding of this basic problem which is one of the underlying factors in the causation of malnutrition in this region where children are fed almost exclusively on plantains, sweet potatoes and cassava.

The mortality rate has been high (20%), but in a complex disease like malnutrition, which develops slowly, it is not likely that treatment, no matter how effective it may be, will immediately alter the widespread damage done to the vital organs. It is not surprising, therefore, that 25 (69%) of the deaths occurred within 48 hours of admission. Another reason why mortality is high is that, because of the limited bed-space only seriously ill cases of kwashiorkor are admitted.

(III) Malaria. Malaria causes many symptoms in children: convulsions, diarrhoea and vomiting, severe anaemia, jaundice and bronchitis; while repeated attacks cause failure to thrive. The finding of parasites in the blood does not solve the problem, as positive blood slides for malaria are often seen as coincidental findings in other conditions. The differential diagnosis of malaria from virus infections and other obscure fevers is still an immense problem in tropical paediatrics.

Blood slides are routinely examined in the ward or in the out-patients' department from almost every child. The different strains of malaria may be found here but, in the present series, malignant tertian malaria has been almost the only parasite recorded.

The following observations have been made from the records:

Age Group (yrs)	0–1	1–2	2–3	3–4	4–5	5–6	6
Cases	71	67	26	8	7	2	—
Deaths ..	11	5	5	2	1	—	—

Eight cases were admitted with malaria in the first three months of life and most of these were Baganda. Davies (1954) noted a highly significant difference between Baganda and non-Ganda in the incidence of malaria in the neonatal period. In the present small series this has not been borne out.

AGE DISTRIBUTION ACCORDING TO TRIBE (UP TO 2 YEARS)

Age Group ..	6 months	1 year	1–2 years
Ganda	17	26	54
Ruanda-Urundi ..	4	2	5
Others	4	14	12

TABLE 13

Month	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
Admissions	8	13	20	15	26	26	18	11	6	11	8	1

TABLE 14

Hb (g./100 ml.) ..	< 4·2	4·2–5·6	5·6–7·0	7·0–8·4	8·4–9·8	9·8–11·2	11·2–12·5
Cases	25	16	12	19	27	21	8

Table 13 shows the number of cases admitted to the ward in each month:

MALARIAL ANAEMIA. Haemoglobin estimations were done in most of the cases and the results are shown in Table 14.

Many of the affected children were very anaemic, but responded to malarial drugs and iron. Fifteen (8%) cases had to be transfused. One child diagnosed as blackwater fever recovered; eight cases were diagnosed as cerebral malaria and of these two died.

ADDED INFECTIONS. Seven cases of malaria also had hookworm infection, two showed ascaris and hookworm and one child had a tapeworm.

(IV) Tuberculosis. The diagnosis of tuberculosis in children is difficult, as sputum is not easily obtained in this young age group. Interpretations of gastric washings, where other acid-fast bacilli may be found, can be misleading, and culture or animal inoculation entails a long delay. In any case, bacteriological facilities are not available at present in sufficient amount to deal with all cases.

The tuberculin test, which is very useful in arriving at a diagnosis in children, often gives results in our patients which are inconsistent. This may be due to many factors but, in the undernourished children with advanced tuberculosis, anergy can develop.

It was by considering the history, clinical examination, the presence of definite or suspicious radiological evidence of tuberculosis, or by deciding to use the therapeutic test that the diagnosis was made in most of the cases.

Seventy-three cases forming approximately 5% of the total admissions were classified as having tuberculosis. Four were of bone (one death), four with glandular involvement (no deaths), and five had tuberculous meningitis (two deaths). Pulmonary tuberculosis accounted for 60 cases with 11 deaths.

The age distribution of tuberculosis cases was as follows:

Age (years) ..	0–1	1–2	2–3	3–4	4–5	5–6	6
Cases	27	22	7	4	7	4	2

HAEMOGLOBIN. This was estimated and the results are given in Table 15.

ADDED INFECTIONS. Blood slides for malaria gave the following results: eight positive, in eight cases it was not done, and the rest were negative.

STOOLS. Twenty were examined and eight showed hookworm ova.

(V) Anaemia. The common causes of anaemia are hookworm, sickle cell disease and malaria. A few cases of unexplained haemolytic anaemia are found. Of cases of anaemia 144 (10·4% of total admissions) can be separated into the following groups: 61 hookworm anaemia (five or 8·3% deaths), 66 sickle cell anaemia and 17 cases of unspecified anaemia (six or 35% deaths). (Malaria anaemia is not considered here, but has been dealt with earlier.)

HOOKWORM ANAEMIA. The diagnosis of hookworm anaemia is arrived at by exclusion of the other two common causes of anaemia and the finding of occult blood in the stool. The finding of a large number of hookworm ova in the stool is very suggestive, but as a combination hookworm infestation, malaria infection, the sickle cell gene (in either the heterozygous or homozygous states) and malnutrition can occur in the same patient; it is often difficult to make a firm diagnosis.

TABLE 15

Hb (g./100 ml.) ..	< 4·2	4·2–5·6	5·6–7	7–8·4	8·4–9·8	9·8–11·2	11·2–12·6
Cases	2	8	11	18	19	6	2

The following age distribution was found in the present series:

Age (years) ..	0–1*	1–2	2–3	3–4	4–5	5–6	6
Cases	8	14	23	7	5	3	1
Deaths ..	1	4	—	—	—	—	—

* The youngest age recorded was 3 months.

Many cases were very anaemic when admitted and this is borne out by the fact that 65·5% of the cases were transfused. There was only one fatal case among those transfused. The other four died because there was no blood immediately available, or so soon after admission that transfusion was not feasible.

SICKLE CELL ANAEMIA. Out of 66 cases who were sicklers, 45 were diagnosed as sickle cell anaemia on the presence of either dactylitis, characteristic radiological bony changes or of Hb S only on paper electrophoresis. Tribal distribution showed 54 Ganda, two Ruanda-Urundi and 10 'others'. Fifteen patients (22%) were transfused.

The age distribution was as follows:

Age (years) ..	0–1	1–2	2–3	3–4	4–5	5–6	6
Cases	26	11	10	6	8	3	2
Deaths ..	2	2	2	—	2	—	—

Twenty-five cases had dactylitis or periosteal bone reaction. In two cases *Salmonella typhimurium* was isolated on culture of the lesion. *Staphylococcus pyogenes* was reported in another two and in one both *Staphylococcus albus* and alpha haemolytic streptococci were found.

Haemoglobin estimations in this group are given in Table 16.

Age (yrs)	6 mths	0·5–1	1–2	2–3	3–4	4–5	5–6	6
Male ..	31	23	35	17	3	5	3	1
Female ..	14	18	17	8	—	—	3	—

It is found that the highest incidence is in the first two years of life. This is also the time when the diseases, such as measles and whooping cough, attack children. It was apparent that many of the pneumonias admitted were complications of measles and whooping cough.

Acute laryngo-tracheo-bronchitis is a disease which has been diagnosed more frequently in Kampala of recent years and carries a high mortality (24%). In addition, out of the 29 cases, tracheotomy was performed in 12 (41%).

(VII) Miscellaneous Group

Meningitis. There were 60 cases of meningitis in this series, of whom 22 died (37%). Twenty-two were caused by *Haemophilus influenzae* (three deaths). There were nine pneumococcal cases with five deaths. In 31 cases of purulent meningitis, in which no organism was isolated, there were 14 deaths. In only one case were meningococci isolated and the patient recovered.

The mortality of 22 (37%) appears high, but must be considered in relation to the fact that many of the patients come in very late and have often been partially and inadequately treated.

Congenital Abnormalities. This group includes congenital abnormalities, for which patients are admitted, and does not give the incidence of minor congenital anomalies in all patients admitted, as they were not specifically looked for or recorded.

There were five cases of congenital heart disease, three of hare lip and cleft palate, three of hydrocephalus, two of spina bifida with meningocele, two mongols (one with congenital heart disease and the other with congenital cataracts), two with congenital laryngeal stridor and one case of each of the following: sacrococcygeal teratoma, hypertrophic pyloric stenosis, exomphalos, cystic hygroma, posterior urethral valves, congenital dislocation of the hip, imperforate anus, ectopic anus, micrognathia, cranofacial dysostosis and arthrogryposis multiplex congenita.

TABLE 16

Hb (g./100 ml.) ..	< 4·2	4·2–5·6	5·6–7	7–8·4	8·4–9·8	9·8–11·2	11·2–12·6	12·6–14
Cases	18	14	12	9	7	2	3	—

(VI) Respiratory Diseases. Diseases of the respiratory system are commonly seen in the out-patients and in the child welfare clinics. Many of them are not admitted but treated as out-patients and only very seriously ill patients are admitted because of the limited bed space. This gives a high mortality rate.

Pneumonias have been grouped together, and showed the following age distribution:

Infection of Skin, Bone and Soft Tissues. There was one case of each of the following conditions: vaginitis, peritonitis, pelvic abscess, cellulitis of leg, pyomyositis and abscess of the neck.

There was only one child diagnosed as having eczema and one with chronic ulceration of the skin of unknown aetiology. Ten newborn babies were admitted with umbilical sepsis.

There were three cases of osteomyelitis (excluding those associated with sickle cell anaemia).

Heart Disease. There were four cases of rheumatic heart disease and all recovered from the acute illness; three cases of congestive cardiac failure of unknown aetiology, one of whom recovered, while two died within 24 hours of admission. One child died of purulent pericarditis, confirmed at autopsy.

Poliomyelitis. Four cases of poliomyelitis were admitted to the ward. None were fatal.

Poisoning. There were 15 cases of poisoning. Eleven were due to kerosene poisoning (two deaths) and two cases each from *waragi* (locally distilled spirits) and probably from mushroom poisoning.

Malignant Tumours. There were five cases of malignant disease in the present series, four were malignant lymphomas and the other was sarcoma of the maxilla. All except one died in hospital.

Renal Disease. There were 18 cases of renal disease, eight acute nephritis and five pyelitis. There were two deaths, one from nephrosis and pneumonia, and the other from congenital cystic kidney, diagnosed clinically as uraemia.

Tetanus. There were 13 cases of tetanus in all age groups with recovery of only two cases. (These figures are biased by the inclusion of 10 cases of tetanus neonatorum, all of whom died.)

Infections. Included in this group are two cases of measles, one of brucellosis, one fatal case of widespread moniliasis of the respiratory and alimentary tracts, and two cases of congenital syphilis, presenting with jaundice and anaemia.

Miscellaneous. Included in this group are five cases of epilepsy, six babies with melaena neonatorum, 10 cases of prematurity, three cases of birth injury and one of the peculiar local form of dwarfism, known as *Nakalanga* (Raper and Ladkin, 1950).

Discussion

The high mortality rate and the difficulties briefly touched on in the present paper leave no doubt as to the magnitude of the problem facing the paediatrician in an underdeveloped tropical country. Luder (1957) ably presented the problems when he gave the results of his two years' experiences in Uganda. There has been no material expansion of the paediatric unit since his time, but there has been a steadily increasing flood of patients, as judged for example, by a six-fold increase in paediatric out-patients in the past six years, and probably also a changing pattern of childhood disease.

In discussing the age incidence of serious disease, it is obvious that the highest morbidity is in children up to 3 years of age. It is the period when children's infections, malnutrition and helminthic infestations are most severe and burdensome. In the tropics, the relationship between malnutrition, infection, poverty and ignorance is so interwoven that it is often difficult to define the exact part contributed by each to the problems of child health.

Certain facts seem to appear as a result of this bird's-eye view of the grosser aspects of paediatric cases seen in Mulago Hospital.

For example, the local aetiology of anaemias still requires further elucidation. There is a group of haemolytic anaemias for which the ordinary haematological investigations do not appear to assist in diagnosis. Inadequate histories always add to the difficulty.

Febrile convulsions are another very common syndrome in young children here. Investigation as to causation, in relation, for example, to cerebral malaria and encephalitis, is much needed.

Obvious neonatal infections are frequent and have a high mortality. The incidence of less obvious syndromes, such as sepsis neonatorum, is unknown.

Poliomyelitis was diagnosed in only four cases admitted to the ward. This is, however, a small figure compared with the continuous trickle of cases seen in the out-patients, who are referred direct to the physiotherapy department. It is clear, in fact, that poliomyelitis is highly endemic in Uganda, and the slowly rising standards of hygiene in some areas can be expected to be followed by actual outbreaks, unless prevented by immunization.

Congenital syphilis is rarely seen either in the out-patients or as a cause for admission. It would, however, come in the differential diagnosis of dactylitis of sickle cell disease, of babies with jaundice or anaemia or failure to thrive. The reason for this apparent rarity is not known, but it seems possible that the widespread use of penicillin, at least in towns, might be relevant.

Probably the most significant trend is that towards a progressively higher incidence of gastroenteritis in young infants. This is mainly associated with a falling off of breast-feeding in the towns, and poses a huge and threatening problem. A rehydration centre at Mulago Hospital is in the process of development.

Many congenital and genetic diseases (apart from sickle cell anaemia) are at present obscured by the mass of 'environmental' paediatrics. It is impossible to concentrate on less common but interesting maladies which are at present missed as a result of the daily scramble to find a bed for the next admission.

There is a real need to assess the present status of child health in Uganda in greater detail. Community studies in different groups are already being carried out, while in order to be able to reassess the situation in hospital with advantage, better hospital statistics are essential in future, ideally with especially prepared proforma suitable for yearly analysis.

In spite of the many difficulties, work under these adverse conditions is interesting and, provided there is balanced progress between preventive medicine and the curative services many of the paediatric problems of today will be overcome as the majority of the admissions are due to preventable diseases. The main need is for health education, which requires development in all directions, in order to break the vicious circle formed by ignorance, malnutrition, disease and poverty.

Unfortunately, neither the public nor those in politics or administration are aware of the huge, but preventable, problems of child welfare in Uganda, so that the necessary emphasis on child health is developing too slowly, but may perhaps gain impetus in the next few years.

Summary

The child morbidity and mortality has been studied by the analysis of admission of children to the Paediatric Division, Mulago Hospital, in 1959. The main causes for admission have been discussed. The tribal, age and sex distributions are noted. The high morbidity and mortality in early childhood are noted and some of the tropical paediatric problems contributing to this high death rate are discussed.

I am most grateful to Professor D. B. Jelliffe and Dr. C. E. Stroud for encouragement and help during the preparation of this paper, and to the Chief Medical Officer, Uganda, for permission to publish.

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CALCIFICATION OF THE ADRENAL GLANDS IN YOUNG CHILDREN

A REPORT OF THREE CASES WITH A REVIEW OF THE LITERATURE

BY

J. STEVENSON, A. M. MACGREGOR and P. CONNELLY

From the University Department of Infectious Diseases, Ruchill Hospital, Glasgow

(RECEIVED FOR PUBLICATION SEPTEMBER 21, 1960)

Calcification of the adrenal glands occurs in other mammals besides man, for it has been recorded after distemper in cats and has also been observed in dogs, rats and monkeys (Marine, 1926; Ross, Gainer and Innes, 1955). Not unnaturally its occurrence in man has been more completely tabulated; it may be produced by tumours or cysts, and its association with haemorrhage, trauma and burns is well documented. So far as tumours are concerned, ganglioneuromas, neuroblastomas, phaeochromocytomas and adenocarcinomas have all been involved in the process (Schwartz and Fink, 1956). It is probable that any of these may be associated with cyst formation and this in turn may encourage haemorrhage into the cyst. Williams (1955), indeed, came to the conclusion that, in the cystic adrenal, haemorrhage was probably the precursor of calcification. Its occurrence as a rare complication in the lipoidoses (Abramov, Schorr and Wolman, 1956) requires a different explanation, and Alexander (1946) suggested that in this condition the calcific deposition could be explained by supposing that the fatty acids released by the hydrolysis of cholesterol esters were saponified by calcium.

With regard to the part infection may play in the production of such calcification, the condition most often thought of is tuberculosis. Other infections, however, have been recorded, the more notable being severe cases of meningococcal, and less often pneumococcal, septicaemia (Prior, 1953). It seems likely that in infection, and where calcification follows severe burning, the common link is the occurrence of haemorrhage into the gland for such bleeding is a common enough complication in all of them.

The importance of haemorrhage is further underlined by the fact that it is known to be a rare complication in the infant as a result of difficult labour and of prematurity. Occasionally the haemorrhage is diagnosed clinically, because of the severe collapse of the newborn infant and in some cases a tumour may be felt in the abdomen. Hill and Williams (1959) reported such a case and listed 25 instances in which massive fatal adrenal apoplexy occurred under such circumstances and another nine who survived the incident.

The fact that it is possible to survive the haemorrhagic incident must suggest that haemorrhage need not always be severe; and it is reasonable to assume that minor degrees of bleeding may escape clinical detection. Snelling and Erb (1935), for example, reported a series of 3,637 consecutive autopsies on infants and on children, in 43 of which (1·19%) haemorrhage into the adrenal gland was found. In only one had it been suspected clinically. Of the total, 15 occurred in infants and 28 in older children. Eight of the total showed evidence of calcification as well as of haemorrhage, one of which was a baby who was 6 days old at the time of death. Seligman (1928) analysed a series of 1,185 autopsies on adults with special reference to the appearance of the adrenals, and found four cases with evidence of calcification in the cortex. He was unable to explain the occurrence satisfactorily and postulated that sublethal haemorrhage might have occurred during the immediate neonatal period.

In trying to understand why haemorrhage should occur in these infants, a number of interrelated factors may be involved. It is well known that the adrenal gland of the newborn infant is relatively large compared to that of the adult and is especially so when the child is premature. The gland undergoes a rapid involution after birth, but before this its size and immaturity must render it more liable to damage. This may occur in relation to an abnormal presentation and the breech variety seems particularly vulnerable (Stevens and Tomsykoski, 1954; Wilkins, 1959). The fact that traction has been applied to the flanks is probably the reason. Then

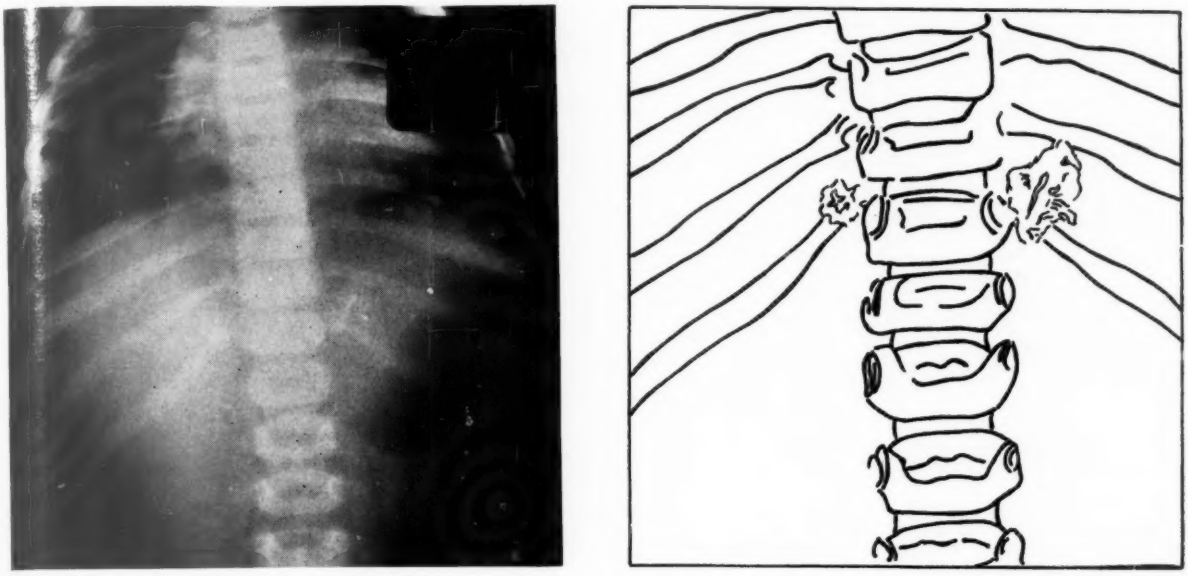


FIG. 1.—Radiograph of the abdomen in Case 1, showing bilateral adrenal calcification. Fig. 1a shows enlarged outline drawing of central area.

again, when there has been foetal distress, the too vigorous application of certain types of resuscitation might easily inflict damage. Finally, the presence of some haemorrhagic disease of the newborn or of asphyxia neonatorum are further aetiological possibilities because of the alterations in the vascularity of the gland which they may produce. That trauma of itself may play a part is suggested by Rack and Eiben (1951) who reported a case of a 2½-year-old child with unilateral haemorrhage and calcification of the adrenal. They postulated that trauma at the time of a severe thrashing known to have been administered six months previously might have been responsible.

Thus the survival of the child seems possible when the haemorrhage has not been severe. Such children may not always show clinical evidence of the condition. In these symptomless cases the diagnosis will usually be made by chance when a radiograph, usually of the chest, which has been taken for other reasons, reveals the abnormality. The three cases which we wish to report fall into this category.

Case Reports*

Case 1. A female child, aged 7 weeks, was admitted on March 11, 1958, as a case of bronchopneumonia. She had been ill for two days with an upper respiratory infection and had then developed a cough, cyanosis and vomiting. Clinical and radiological examination confirmed the presence of pneumonia and the child responded well to chemotherapy. The chest radiograph was of sufficient size to take in the upper abdomen where bilateral calcified adrenal glands were seen (Fig. 1). Clinical reappraisal in the light of this finding showed no obvious sign of adrenal insufficiency. The Mantoux reaction was positive, but the child had been given B.C.G. at birth. Serum tested for toxoplasmosis gave negative results. The child was discharged well on April 6, 1958.

The obstetric history was normal. The child was a vertex delivery after a surgical induction done just before term because of contracted pelvic outlet. Labour lasted seven and a half hours, but no foetal or maternal distress was noted. The birth weight was 7 lb.

Periodic assessment since dismissal has shown that the child is thriving. There seems, however, to be an increased susceptibility to upper respiratory tract infections. Radiographs taken recently suggested that the suprarenal calcification may have increased. In order to gain some objective evidence of adrenal function blood steroid levels and circulating eosinophils were measured before and four hours after an intramuscular injection of 40 international units of A.C.T.H. with the following results:

	Before A.C.T.H.	*Four hours after A.C.T.H.*
(1) Plasma 17-OH corticoids ..	0 μg./100 ml. of serum	37·5 μg./100 ml. of serum
(2) Eosinophil count	22 per ml.	6 per ml.

* In these case notes no reference has been made to any blood pressure readings. These were done by using an appropriate size of sphygmomanometer cuff, the levels being measured by auscultation and the flush technique. The readings were as a rule higher than one might expect at the appropriate ages, but as readings are notoriously difficult to assess accurately in young children without direct arterial puncture, the figures have been omitted from the text.

Case 2. A female child, aged 2 years, was admitted on May 12, 1958, for investigation of an unexplained fever. Clinical and radiological examination revealed a left basal pneumonia; penicillin was given and rapid improvement ensued. As in Case 1, the chest radiograph took in sufficient of the upper abdomen to show bilateral adrenal calcification (Fig. 2). No evidence of adrenal insufficiency could be found and Mantoux skin tests were negative. She was discharged well on June 2, 1958.

The obstetric history showed the child to have been five weeks premature and a brow presentation. Delivery was spontaneous; the birth weight, 5¼ lb. She was initially cyanosed and slow to respond to resuscitation and as a result was kept in a premature baby nursery where recurrent cyanotic episodes were noted. Finally, however, she thrived.

She has kept fairly well since dismissal, although there have been frequent episodes of upper respiratory infection and an attack of whooping cough.

Between November 18, 1959 and December 3, 1959, she was readmitted for further assessment. On this occasion it was noted that the skin was dry and that there was some flattening of the vault of the skull. Observation over this period also showed that she had an ataxic gait and appeared mentally retarded. There were, however, no localizing signs on examination of the central nervous system.

Radiographs of the skull were normal and an E.E.G. was regarded as within the normal limits for her age. An intravenous pyelogram was normal and confirmed the calcification to be adrenal in site. Biochemical assessment included liver function tests, serum electrolytes, calcium, phosphate, cholesterol and urea levels, all of which were normal. Fasting blood sugar was 80 mg./100 ml. Electrophoresis of the serum proteins and chromatography of the urine were normal. The urine was also normal on chemical and microscopic examination. Serum tested for toxoplasmosis was negative.

As in Case 1, the response to an intramuscular injection of 40 international units of A.C.T.H. was assessed and in this case steroid levels in the urine were also measured.

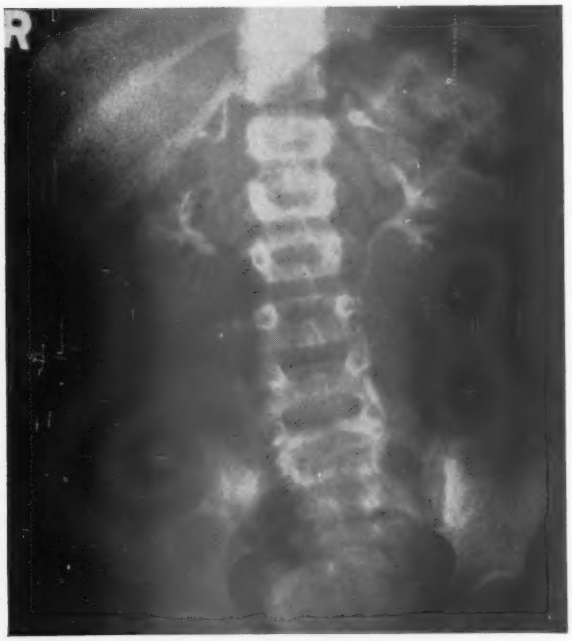
	Before A.C.T.H.	*Four hours after A.C.T.H.*
(1) Plasma 17-OH corticoids ..	10 μg./100 ml. of serum	21 μg./100 ml. of serum
(2) Eosinophil count	154 per ml.	90 per ml.

24-hour collection of urine before the test:
Total volume, 615 ml.; 17-ketosteroids, 0·75 mg. per day; total 17-OH corticoids 4·3 mg. per day.

24-hour collection of urine after A.C.T.H.:
Total volume, 590 ml.; 17-ketosteroids, 0·8 mg. per day; total 17-OH corticoids, 5·4 mg. per day.

Case 3. A male child, aged 1½ years, was admitted on May 7, 1959, suffering from measles complicated by bronchopneumonia. It was noted at this time that he had a dry eczematous skin and that the liver was enlarged to about two-finger breadths below the right costal margin. Response to penicillin was poor and as the radiographic appearances suggested the possibility of a staphylococcal pneumonia, a combination of chloramphenicol and erythromycin was given with satisfactory resolution.

The enlargement of the liver subsided with recovery



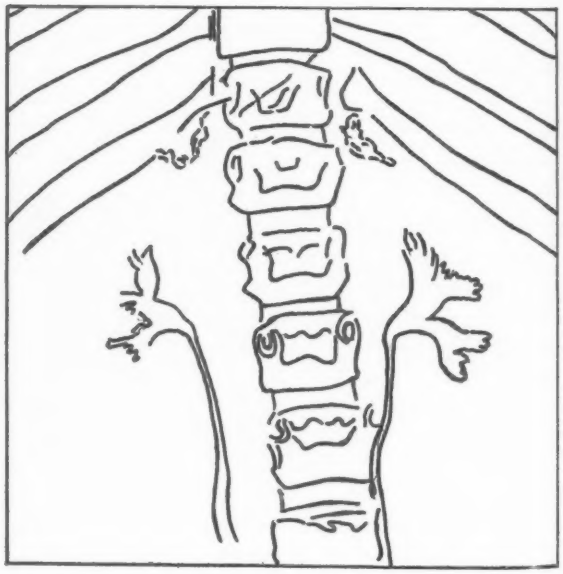


FIG. 2.—Radiograph of abdomen in Case 2. This shows a rather different pattern of distribution of the calcification, the film being taken at the time of an intravenous pyelogram. Fig. 2a is an enlarged outline.

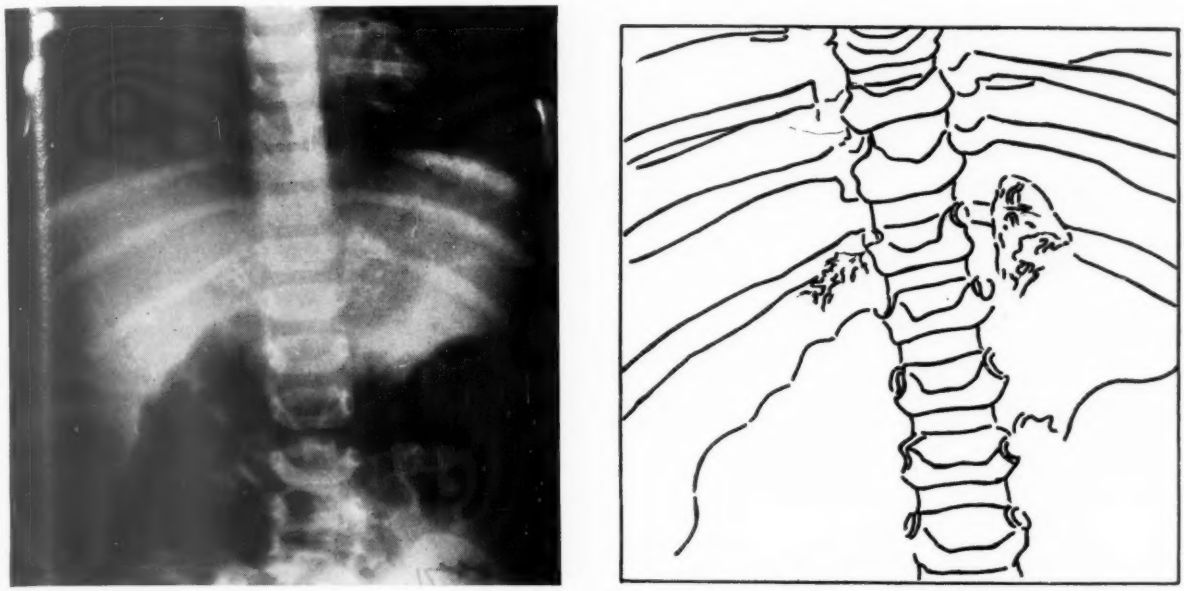


FIG. 3.—Radiograph of abdomen in Case 3 showing greater areas of calcification than in other cases, especially on left side. Fig. 3a is an enlarged outline.

from the infection, but a radiograph of the abdomen showed bilateral calcification of the adrenal glands (Fig. 3). Since there was no evidence of associated adrenal insufficiency he was dismissed on August 13, 1959. Mantoux skin test was negative as was examination of the serum for antibodies to toxoplasma.

Obstetric history showed that the child was a normal presentation with an uneventful labour. The child was, however, three weeks premature, weighing 4 lb. 12 oz. He was treated in a premature baby unit, but no asphyxia was reported.

On November 3, 1959, he was readmitted because of obstinate bronchospasm which settled after treatment with a variety of antispasmodics. A further chest radiograph showed signs of early emphysema and clinically the thorax was becoming barrel-shaped. Biochemical assessment showed normal values for the serum electrolytes, urea, calcium and phosphate, and liver function tests. The electrophoretic pattern was normal and a fasting blood sugar 123 mg./100 ml.

The response to 40 international units of A.C.T.H. in this case was as follows:

	Before A.C.T.H.	*Four hours after A.C.T.H.*
(1) Plasma 17-OH corticoids ..	5 μg./100 ml. of serum	17·5 μg./100 ml. of serum
(2) Eosinophil count	36 per ml.	22 per ml.

Discussion

In the three cases described above, bilateral adrenal calcification has been found by chance and, in view of the age of the patients and the lack of evidence to indicate another aetiological factor, it seems reasonable to suggest that haemorrhage at, or just after, birth was the initial cause. None of our cases has shown clinical evidence of hypoadrenocorticism, and although adrenal function tests are difficult to perform in young children and there is a wide range of normality, our own figures after A.C.T.H. stimulation do not indicate any gross deficiency. Perhaps one should not suspect any impairment of adrenal function since the presence of the calcification does not necessarily imply widespread destruction of adrenal tissue. Even if it did, Sézary (1923) has suggested that up to 90% of adrenal tissue can be destroyed and survival can still be possible. A certain amount of functioning adrenal tissue can be found in the testes and ovaries and this may play a part in offsetting the loss of the adrenal glandular secretions. Despite the present good health of our own cases, it is important to appreciate that this condition has been reported in association with a variety of clinical pictures and in a few instances it has been claimed to have caused death. A continued follow-up of our own cases is, therefore, desirable.

A survey of the literature indicates that the condition may not always be benign. Death in coma after convulsions, sometimes of an epileptiform nature, has been reported in three instances (Newsan (1924) in a child of 2½ years; Lintz (1943) in a child of 11 years; Minder (1954) in a case aged 28 months). Gardner (1957) reported two living examples; one

of these had skin pigmentation and required hydrocortisone supplements during any infectious episodes. This case, a premature breech delivery complicated by asphyxia, had low serum steroid levels which rose, however, after A.C.T.H. stimulation. His second case, with a normal obstetric history, also had crisis-like episodes with infection and in this case there was associated hypoglycaemia.

Does the calcification persist or increase with the chance of trouble later on? Seligman (1928) suggested that the calcification he found in his four adults may have been there throughout life. On the other hand, Drucker and Rodriguez (1955) thought the calcification in their case increased over some months before the child died from a respiratory infection and Lintz's case had signs of adrenal insufficiency from the age of $2\frac{1}{2}$ years before finally dying at the age of 11. In our own Case 1 serial radiographs suggest a slight degree of extension, though this could be simply a redistribution of calcium with growth.

The case reported by Schwartz and Fink (1956) was of special interest to us. A 9-month-old baby was admitted with fever, vomiting and respiratory difficulty, and subsequently died. At autopsy, calcification and ossification of the adrenal glands were found and the lungs showed acute generalized obstructive emphysema. We have been impressed by the early development of emphysema in our own Case 3 and have wondered whether there is a cause-and-effect relationship. It is true that many of the cases reported with this adrenal abnormality had an associated respiratory infection, and this is true of our own three cases; this association might be explained quite simply by the fact that the chest radiograph often brings the calcification to light.

In view of the reported association of haemorrhage and calcification, it was considered of interest to review some cases of severe adrenal haemorrhage (Waterhouse-Friderichsen syndrome) treated in this hospital for meningococcaemia. Accordingly, we carried out a review of 21 cases treated over the past six years. These patients had shown extensive skin haemorrhages associated with collapse and required steroid therapy during the acute phase of the illness. Their ages ranged from 5 months to 14 years at the time of the fulminating infection. In none did we find any evidence of adrenal insufficiency and on the radiographs none showed evidence of calcification.

In conclusion it might be worth suggesting that some cases can be prevented by such measures as care in dealing with abnormal, and especially breech, presentations, by the avoidance of undue force in measures of resuscitation and by the prompt treatment of any asphyxia.

Summary

Three cases of bilateral calcification of the adrenal glands in infants are described. The pathogenesis of the condition is discussed and the most usual cause is thought to be haemorrhage at, or about the time of, birth.

Factors such as prematurity, abnormal presentations and abnormal labour, asphyxia, or a combination of any of these, seem to predispose to such haemorrhage and some cases could probably be prevented by good obstetrics.

In those cases where the finding has been made during life it has usually been unsuspected. While it may often be of little importance in some children, it seems to be associated with definite signs and symptoms which may declare themselves in the form of an increased response to infection or stress of any kind, by focal or generalized epileptiform seizures, by hypoglycaemia and as classical Addison's disease with pigmentation.

It is hoped to maintain contact with the patients in order to observe their progress.

We would like to thank Professor T. Anderson and Dr. J. H. Lawson for permission to publish these cases. We are also indebted to Dr. W. G. Whyte of the Royal Infirmary, Glasgow, for the blood steroid estimations.

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THE EFFECT OF A CONTINUOUS INTRAVENOUS INFUSION OF INORGANIC PHOSPHATE ON THE RACHITIC LESIONS IN CYSTINOSIS

BY

ROBERT STEENDIJK

From the Department of Paediatrics, University of Amsterdam

(RECEIVED FOR PUBLICATION SEPTEMBER 19, 1960)

Fraser, Jaco, Yendt, Munn and Liu (1957) and Fraser, Geiger, Munn, Slater, Jahn and Liu (1958) reported healing of rachitic lesions in vitamin D-deficient and in hypophosphataemic refractory rickets by intravenous administration of phosphate. The concentration of serum inorganic phosphorus, which initially had been very low, was kept at normal levels for a period of five to seven days. The authors concluded that vitamin D was not obligatory for healing in these types of rickets.

The metabolic defect in cystinosis leading to severe amino-aciduria, glycosuria, metabolic acidosis and deposition of cystine crystals in various organs, in addition to hypophosphataemia and rickets, is undoubtedly more severe than in infantile and primary refractory rickets. But there is no valid reason to suppose that the pathogenesis of rachitic lesions is different from that in other types of rickets, in which an insufficiency of calcium and a low concentration of serum inorganic phosphorus inhibit proper calcification of the bone matrix. However, this has never been proved. It was therefore decided to find out whether improved calcification could be obtained by inducing a lasting rise in the concentration of serum phosphorus in the absence of vitamin D and alkalizing agents. Simultaneously, the effect of the induced rise in the concentration of serum phosphorus on the concentration of serum calcium and on the product of these concentrations was studied.

Case Report

The subject of this investigation was a 9-month-old boy, the fifth child of healthy parents who were first cousins. At the age of 6 months the first symptoms of the disease appeared (polyuria, polydipsia, failure to thrive); two months later he entered the Children's Hospital. On admission, physical examination revealed moderate malnourishment, craniotabes, rachitic rosary and thickening of the wrists. A slit-lamp examination of the cornea revealed the presence of numerous tiny crystals. Radiographs of the skeleton showed severe rickets.

Serum concentrations of calcium and inorganic phosphorus were 10·0 and 1·9 mg./100 ml. respectively; the serum level of alkaline phosphatase was 17·8 Bodansky units. Plasma sodium, potassium and CO_2 combining power were 137·0, 4·0 and 13·5 mEq/litre respectively. Results of liver function tests (thymol turbidity and cholesterol partition) were within normal limits. The creatinine clearance was 100 ml./min./1·73 sq. m. The specific gravity of the urine varied between 1,010 and 1,014; the 24-hour volume ranged from 600 to 800 ml. The urine contained a trace of albumen and 0·5 to 1% of reducing substances; the ratio amino-N to total N was 0·19.

Methods

Serum phosphorus was determined according to the method of Briggs (1922). Serum calcium was estimated colorimetrically by titration with ethylene diamino tetra-acetate, using murexide as indicator.

For the infusion a sterile stock solution was prepared containing 1·8807 g. of Na_2HPO_4 2 aq. and 0·4502 g. of NaH_2PO_4 2 aq. per 100 ml. of water. The *p*H of this solution was 7·3; it contained 416·6 mg. of inorganic phosphorus per 100 ml. and it was isotonic with blood.

The total volume infused per 24 hours was 500 ml. It consisted of a mixture of 5% dextrose in water and the phosphate solution. The amount of phosphate infused initially was 750 mg. per 24 hours. Later it was derived by trial and error from the concentration of serum phosphorus, which was determined at least once every day. The aim was to obtain a serum level of at least 3·5 mg./100 ml.

The fluid was administered by way of a polyethylene catheter which had been introduced in a saphenous vein. The rate of flow was kept constant throughout the time the infusion lasted.

Results

The effects of the infusion of inorganic phosphate on the serum levels of calcium and phosphorus are presented in the Table and Fig. 1. The induced

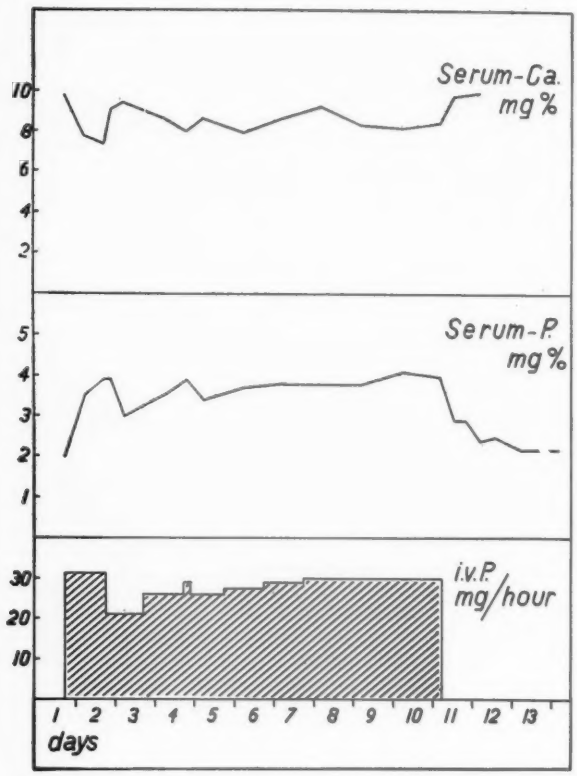

FIG. 1.—Relation between serum levels of calcium and phosphorus and rate of phosphate infusion.

TABLE

EFFECT OF CONTINUOUS INTRAVENOUS INFUSION OF PHOSPHATE ON SERUM LEVELS OF CALCIUM AND INORGANIC PHOSPHORUS

Day	Time	Serum/ Calcium (mg./100 ml.)	Serum/ Phosphorus (mg./100 ml.)	Intravenous Phosphate Solution (mg./hr)
1	17.00	9·8	2·0	31 (start infusion)
2	9.30	7·8	3·5	
	17.00	7·4	3·9	21
	22.00	9·1	3·9	
3	9.30	9·4	3·0	
	17.00			26
4	9.30	8·7	3·5	
	17.00			29
	21.00	8·0	3·9	
	22.00			26
5	9.30	8·7	3·4	
	17.00			27·5
6	9.30	8·0	3·7	
	17.00			29
7	9.30	8·7	3·8	
	17.00			30
8	9.30	9·3	3·8	
9	9.30	8·4	3·8	
10	9.30	8·3	4·1	
11	9.30	8·5	4·0	(stop infusion)
	15.00	9·8	2·9	
	21.00	9·9	2·9	
12	9.30	10·0	2·4	
	15.00		2·5	
13	9.30		2·2	
14	9.30		2·2	

rise in serum phosphorus was accompanied by a corresponding fall in serum calcium. Subsequently, serum calcium rose slightly but did not attain its previous normal value until the infusion ceased. The infusion was continued for 10 days; two days later serum phosphorus reverted to its previous low value.

Radiographs of the right wrist were taken before the infusion, seven days after the beginning of the infusion, two days after the infusion had been discontinued and one week later. After seven days no signs of improved calcification were visible (Fig. 2a and b). Distinct lines of Mueller were present on the next radiograph however (Fig. 2c). After another week, during which no treatment was given, there was only negligible further deposition of bone salt (Fig. 2d).

Subsequent administration of vitamin D (50,000 I.U. per day) led to additional improvement, but complete healing was not achieved (Fig. 2e and 2f).

The moderate acidosis and the intense aminoaciduria persisted during the administration of phosphate.

It can be concluded that the metabolic defect in cystinosis does not prevent increased deposition of bone salt at the rachitic metaphyses after intravenous administration of phosphate in the manner described and in the absence of vitamin D.

Discussion

Hypocalcaemia. It is not easy to explain satisfactorily the hypocalcaemia which accompanied the induced rise in serum phosphorus. In normal individuals and in patients with primary hyperparathyroidism, given a large intravenous phosphate load, serum calcium shows a slight decrease which is corrected spontaneously within a very short time (Haak and Steendijk, 1960). After a large oral phosphate load serum calcium drops to very low levels in patients with vitamin D deficient rickets, but does not decrease in normal children (Jonxis, 1959). Apparently, the mechanism which maintains serum calcium at a normal level in the face of a rise in serum phosphorus is interfered with in rachitic conditions. Whether this should be ascribed to a diminished response of bone to endogenous parathyroid hormone (Jonxis, 1959), a different solubility of bone salt in rickets (Nicolaysen and Eeg-Larsen, 1956; Sobel, 1953), or a limited availability of calcium (Howard, 1953) is not known at present.

Source of Calcium Deposited. From the data obtained it cannot be concluded whether only a redistribution of skeletal calcium occurred, without

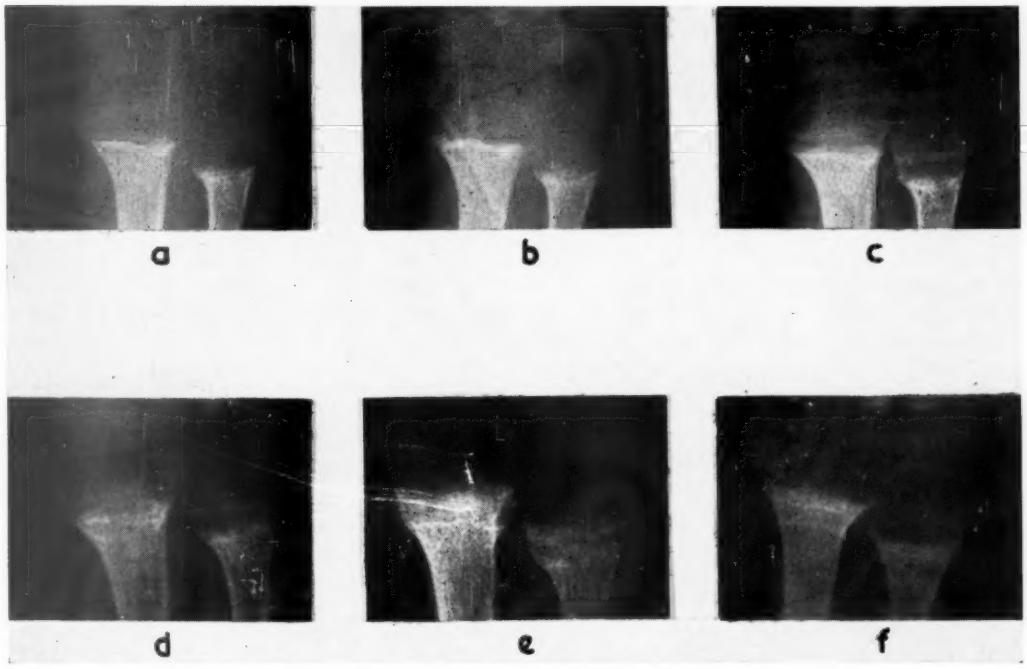

FIG. 2.—Radiographs of the right wrist.

(*a*) Before phosphate infusion.
(*b*) On seventh day of phosphate infusion.
(*c*) Two days after phosphate infusion.
(*d*) 10 days after phosphate infusion.
(*e*) After three weeks of subsequent treatment with vitamin D.
(*f*) After nine weeks of subsequent treatment with vitamin D.

change in retention, or, whether in addition, retention improved due to diminished urinary excretion or increased intestinal absorption of calcium.

Rate of Calcification. Approximately 40 years ago it was established empirically that the product of the concentrations of calcium and inorganic phosphate in serum (Ca × P product) served as an index for the presence or absence of rickets. If the value of this product was too low, i.e. below 30, it was thought that bone salt could not precipitate, thus leading to the development of rickets (Howland and Kramer, 1921). Recently it has been established that precipitation in the true sense of the word does not occur in bone. The mechanism by which the crystals are deposited is a different one, involving catalysed crystal nucleation, the precise nature of which is still a matter of dispute (Neuman and Neuman, 1958; Glimcher, 1959). All the same, it is now known that the rate of calcification (or the rate of nucleation and subsequent crystal growth) increases with an increasing ion-activity product of calcium and phosphate in the fluid bathing bone. At a fixed *p*H and ionic strength, the relationship between this product and the former Ca × P product is a linear one (McLean and Urist, 1955). Therefore the Ca × P product is a reliable index for the rate of calcification and has lost none of its previous usefulness.

Parenthetically it must be stated that the Ca × P product is not valid as an index for the rate of calcification in conditions of rickets associated with a severe glomerular insufficiency.

In the patient described the value of the Ca × P product before the infusion was 19·6, indicating a very slow rate of calcification and the presence of severe rickets. The average values for the concentrations of calcium and phosphorus during the infusion were 8·7 and 3·5 respectively; the average Ca × P product was 30·4. In normal children of the same age this product is about 50; moderate rickets is present at a value of 30. Even so, by a rise of the product from 20 to 30, the rate of calcification was markedly increased, considering the fairly rapid appearance of lines of Mueller on the radiographs.

From experiments *in vitro* (Thomas, Connor and Howard, 1956; Sobel, Burger and Nobel, 1958), it was concluded that for initiation of calcification of rachitic cartilage a higher Ca × P product was necessary than for crystal growth once crystal nuclei had been deposited. Rachitic cartilage was found to show a considerable degree of calcification

in solutions in which the Ca × P product was low, if brief, previous incubation in a more concentrated solution had taken place. Mere incubation in a weak solution resulted only in a slight degree of calcification. These observations led to the supposition that in clinical rickets 'intravenous infusion of phosphate for short periods might accomplish a benefit for the skeleton far beyond the short duration of the effects evident by alteration of the serum' (Thomas *et al.*, 1956).

From our results a continuation of the fairly rapid rate of calcification, which occurred during the infusion, was not apparent one week after the infusion had been discontinued (Figs. 2c and 2d). Although comparison of the degree of calcification by radiography is a rough method, the similarity of Figs. 2c and 2d rules out anything but a very slight difference. Apparently conditions *in vivo* are different from the conditions prevailing in the experiments *in vitro* quoted above.

By the daily administration of 50,000 I.U. of vitamin D, which was started 10 days after the infusion had been discontinued, the Ca × P product was again increased to 30 and maintained at this level. As expected, although further consolidation of the initial improvement was induced, the value of the Ca × P product was too low for complete healing (Figs. 2e and 2f). As administration of larger amounts of vitamin D led to hypercalcaemia and could not therefore be continued, it was impossible to achieve complete cure.

Summary

Continuous intravenous infusion of inorganic phosphate, causing a substantial rise in serum phosphorus, led to improvement of the rachitic lesions in a 9-month-old boy, suffering from cystinosis.

This shows that the disturbance of calcification in this disease is the result of a deranged metabolism of calcium and phosphate, as in other less complicated types of rickets.

The data obtained are discussed with reference to the modern concepts of the mechanism of calcification.

The help of Dr. R. P. Mesker and Dr. S. de Vries (Department of Ophthalmology, University of Amsterdam) with the slit-lamp examination of this patient, and of Dr. J. C. de Jong and Dr. L. A. Donk (Pharmacy, Binnengasthuis, Amsterdam) with the preparation of the phosphate solution, is gratefully acknowledged.

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CREATINE, CREATININE AND TOTAL BODY POTASSIUM IN RELATION TO MUSCLE MASS IN CHILDREN

BY

W. P. KENNEDY*

From The Hospital for Sick Children, Great Ormond Street, London

(RECEIVED FOR PUBLICATION AUGUST 17, 1960)

The purpose of this paper is to report an investigation in children in which determinations of the 24-hourly creatine and creatinine excretion and the total body potassium measurements were correlated with attempts at estimation of total muscle mass by soft tissue radiography and by body measurements. Although studies on creatinine excretion in children have been done before, to the best of our knowledge, no one has investigated such a correlation.

Creatinine, the internal anhydride of creatine, is relatively evenly distributed in low concentration throughout the water of the body and regularly found in the urine. It has always been assumed that creatinine excretion is related to the muscle mass of both children and adults and there have been several studies to show that there is a constant relationship to body weight in lean individuals and to the expected weight in the obese (Muldowney, Crooks and Bluhm, 1957; Garn and Clark, 1955). Creatinuria is found regularly in children, diminishing quantitatively as the child grows older, but varying considerably from day to day (Beard, 1943). Catherwood and Stearns (1937) have shown that in infants and children there is a constant output of preformed creatinine from day to day and this increases as the child grows, presumably due to the increase in muscle mass.

Total body potassium increases with body growth until it reaches adult levels when growth terminates. Because the muscle of the body represents the largest active cellular mass, one assumes that the major fraction of body potassium is related to the total muscle. The value for total body potassium per kilogram varies widely from child to child, and we hoped to find close correlation between total body potassium and total muscle mass, thus enabling a better prediction of total expected body potassium to be made in cases where a loss of potassium was suspected.

Tanner (1955) has shown that as the child grows there is a constant increase in muscle as measured by his technique. This method, which we used, does not give an absolute figure for muscle mass but can only be used as an index which could be related to total body potassium. At the present time there is no method for calculating the absolute muscle weight in children.

Muldowney *et al.* (1957) used the Pace-Rathbun formula for calculating lean body mass (all tissues except fat) in normal adults.

They found a close correlation between total exchangeable potassium, creatinine excretion and lean body mass. We did not feel justified, however, in using a method traumatic to the child in order to calculate muscle mass.

There are certain limiting factors in dealing with infants which make it impossible to include them in the complete study, since the techniques used for the older children cannot be applied satisfactorily to the infant. It is difficult to collect urine from toddlers who will not tolerate the use of the ordinary collecting apparatus used for the infants, and who may still be incontinent. The principal study therefore includes all those children over the age of 6 years. A partial study of creatinine and total body potassium only was made in some infants.

Material and Methods

The children investigated were between 3 months and 13 years of age and were selected from in-patients who had no acute illness at the time. Febrile illnesses and diseases primarily affecting muscles, as well as certain metabolic diseases such as those involving the thyroid, alter the creatinine metabolism and therefore the excretion levels. All children with renal disease were excluded, but we did not consider that confinement to bed made any appreciable difference to our investigation. The conditions for which the children were admitted, and which were quiescent at the time, were asthma, gastro-enteritis, cirrhosis of the liver, chronic constipation, epilepsy, fibrocystic disease of the pancreas, bronchiectasis, psoriasis and eczema.

* Present address: Paediatric Unit, St. Mary's Hospital Medical School, London.

As a preliminary, the method of Folin for the estimation of creatine and creatinine in the urine was checked carefully. It was found that Analar grade of picric acid was suitable without recrystallization. The standard creatinine solution was kept out of direct light and preservative, such as merthiolate, to prevent bacterial contamination, was added. If these precautions were not adhered to marked deterioration occurred in the standard, and straight line calibration curves could not be obtained. Strict temperature control when making the colorimetric reading is very important. A temperature of 20° C. gave the most satisfactory colour development using a 602 filter in an E.E.L. colorimeter, but the time for optimum colour development was 25 minutes and not 15 minutes.

The investigation was carried out in three parts. The first was the estimation of creatine and preformed creatinine in the 24-hour urine. The specimens were collected from 8 a.m. to 8 a.m. on two successive days or in some cases a few days apart. This was done to check the work of others who had shown that the preformed creatinine output was consistent for any given individual. It was found that no shorter period than 24 hours, such as four or eight hour collections, showed any constant result for creatinine (Best, Kuhl and Friedemann, 1952). To obtain the total creatinine value the urine was autoclaved with picric acid at 115°-120° C. for 20 minutes. The method for estimating the muscle mass was that used by Tanner (1955). Measurements were made of height and weight, shoulder and pelvic width, arm and thigh circumference and subcutaneous fat by skin-fold technique. Radiographs of upper arm, lower leg and thigh were also taken for soft tissue measurement.

Total exchangeable potassium was determined by W. W. Payne, by giving 1 microcurie of K^{42} per kg. by mouth and determining the specific activity of the urinary potassium 12 and 24 hours later, using a well-type scintillation counter. It is hoped to report this work in detail later.

Forty children were used for the first part of the investigation, and the results are given in Table 1. In only 13 children was a complete study made (Table 2) and their ages were from 6 to 11 years.

The figures in column 1 of Table 2 represent the total body potassium in mEq/litre/kg. body weight and are arranged in order of magnitude. The value for muscle was arrived at by taking the average of the three measurements of muscle from the soft tissue radiographs, i.e. thigh, lower leg, upper arm. This does not represent

TABLE 1

DAY TO DAY VARIATION IN PREFORMED CREATININE IN 40 CHILDREN

Age (years)	Preformed Creatinine (mg./24 hrs)		Per cent Variation	Mean Creatinine Index
	First Period	Second Period		
3–12 mths	39·0	33·6	0·6	
	43·6	45·2	1·8	
	56·7	68·1	9·1	10·5
	126·3	128·5	0·9	
	136·8	133·5	1·1	
1–3	93·4	88·5	2·6	
	100·0	116·3	7·5	
	118·2	111·5	2·09	12·2
	119·1	120·1	0·4	
	248·5	258·4	2·05	
	251·0	262·5	2·2	
3–6	160·0	158·3	0·5	
	214·2	244·0	6·0	11·3
	224·2	264·4	8·2	
	265·2	277·5	2·2	
6–9	232·0	288·5	10·9	
	332·0	378·3	6·5	
	338·4	313·0	3·9	
	361·8	332·2	4·2	
	340·0	307·5	4·0	
	390·5	443·7	6·3	
	394·4	410·5	1·9	17·0
	420·4	439·6	2·1	
	426·4	487·2	4·4	
	453·0	488·8	3·8	
	466·2	450·2	1·7	
	472·0	419·1	5·4	
	577·1	560·6	1·4	
	690·1	699·2	1·4	
9–13	68·8	55·5	10·6	
	290·0	344·0	8·5	
	293·0	324·0	5·0	
	575·0	560·0	3·4	
	585·0	522·5	5·6	14·3
	592·8	617·1	2·0	
	594·5	569·4	2·1	
	604·2	608·3	0·06	
	613·6	400·5	1·0	
	636·5	632·9	0·2	
	869·0	814·0	3·2	

TABLE 2

CREATINE, CREATININE AND TOTAL BODY POTASSIUM IN RELATION TO MUSCLE MASS IN 13 CHILDREN AGED BETWEEN 6 AND 11

Potassium (mEq/litre/kg.)	Muscle Index	Muscle Corrected	Preformed Creatinine (kg./24 hrs)	Creatine (kg./24 hrs)	Height : Weight Ratio	Subcutaneous Fat
37·0	4·330	3·723	19·8	3·2	4·0	4·6
40·3	5·950	3·808	18·7	6·2	5·1	8·0
42·6	4·286	8·614	21·9	4·0	6·5	3·23
43·3	5·618	6·741	15·5	3·1	5·4	4·5
44·6	5·295	8·207	6·4	5·3	5·2	3·35
45·4	3·811	7·622	13·9	3·5	6·4	3·2
46·0	6·260	5·821	11·9	2·6	4·3	4·6
47·0	5·400	5·616	16·1	4·3	4·6	4·4
49·5	5·769	9·115	20·8	7·4	5·4	3·4
49·5	5·098	7·035	15·4	2·2	5·0	3·6
50·6	4·685	4·872	17·1	3·4	5·2	5·0
51·5	5·100	6·420	20·8	3·7	4·8	3·08
53·0	5·481	4·275	13·8	2·7	6·4	8·2

TABLE 3
WEIGHT AND AGE IN RELATION TO CREATININE INDEX

Age (years)	No. of Cases	Mean Creatinine Index	Range	Average Weight (kg.)	Mean Creatinine Index (Other Authors)	Mean Weight (kg.)
3–12 mths	5	10·5	6·5–13·5	7·1	12·5	7·4
1–3	6	12·25	10·5–14·0	10·2	12·4	—
3–6	4	11·3	8·6–14·0	17·0	20·4	18·9
6–9	14	17·0	15·6–18·4	23·5	24·9	29·4
9–13	11	14·3	12·2–16·4	34·5	24·4	37·2

an absolute figure for muscle mass, but only a relative one for comparison between different ages and sizes. A correction for height and weight and subcutaneous fat was applied to the muscle figure by taking the height : weight ratio and dividing this by the average of the measurements for subcutaneous fat. The result of this is to be found in the column headed 'Muscle Corrected'.

Results

From Table 1 it will be seen that the day-to-day variation in preformed creatinine is relatively small; the variation averages 3·5% in the 40 children studied. In Table 3 weight as well as age have been tabulated with the creatinine index. The output increases with age and weight but does not accord with the published values for normal children (Harding and Gaebler, 1922). There is, unfortunately, no complete set of figures of one investigation covering the age range which we have investigated.

It is clear from our figures that a child at complete rest who has recently suffered some acute illness does not have an entirely normal metabolism of creatinine as judged by the published work of other authors. The figures for creatine output are not included as there is no constancy, there being a marked variation from day to day and no close correlation with age and weight. This same lack of correlation was found for the total creatinine output. Table 3 shows that there is no correlation whatsoever between total body potassium and the 24-hour creatinine excretion or the muscle index, either alone or corrected for height, weight and subcutaneous fat.

This investigation was designed to find a single, clinically applicable method for estimating the expected total body potassium without having to resort to all the techniques used here. If our assumptions and methods are correct, then no correlation could be found between creatinine excretion, total exchangeable potassium and an index of muscle mass.

Summary

Duplicate 24-hour preformed creatinine and creatine excretion levels were estimated in 40 convalescent infants and children. The creatinine output for each individual was reasonably constant, but somewhat lower than the figures reported by other investigators for children over 3 years of age. The total creatinine and creatine outputs showed much greater variation, i.e. the creatine was more variable. In 13 children in addition, an attempt to estimate muscle mass was made by the following methods: measurement of weight, height, limb girth and fat thickness; measurement of muscle shadow in soft tissue radiographs; estimation of total exchangeable potassium using K^{42}. No correlation could be found between creatinine index, estimation of muscle mass from body measurements, estimation of muscle mass from soft tissue radiograph measurements and total exchangeable potassium.

I wish to thank Dr. W. W. Payne for his kindly interest and encouragement both at the time this work was carried out and in the preparation of the paper. I would also like to express my appreciation to the Research Committee of The Hospital for Sick Children, Great Ormond Street, for allowing me to work at the Hospital in the capacity of an Honorary Research Fellow and for the financial aid I received.

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CEREBRAL PALSIED TWINS

BY

ELSPETH M. RUSSELL

From the Department of Child Life and Health, Edinburgh, and Edinburgh Clinic, Scottish Council for Care of Spastics

(RECEIVED FOR PUBLICATION OCTOBER 17, 1960)

Various studies on the prevalence of twins in the cerebral palsied population have shown that twins are more likely than single born children to be affected by cerebral palsy (Asher and Schonell, 1950; Skatvedt, 1958; Hansen, 1960). Berg and Kirman (1960) showed that the proportion of twins among mental defectives exceeded that in the general population. The stillbirth and neonatal mortality rates for twins are three times higher than those for single births (Yerushalmy and Sheerar, 1940). It seems probable that many of the factors which are operating adversely in multiple pregnancies, causing children to be stillborn, to die neonatally or to be mentally defective are similar to those acting in multiple pregnancies resulting in cerebral palsied children.

In the present study of 44 cerebral palsied twins, an attempt is made to elucidate some of these factors.

Materials and Methods

The records of all cerebral palsied patients, who were one of twins, were extracted from the out-patient files of the Edinburgh clinic for the Scottish Council for the Care of Spastics. Cerebral palsied children from any part of Scotland may be referred to this clinic by general practitioners and medical officers for assessment by a medical panel. The patients studied were, therefore, a preselected group.

Of the 488 patients who were examined at the clinic between 1949 and 1956, 45 were one of twins and one was the middle born of triplets.

Data were obtained from the clinic's records, from maternity hospital records and by personal interview with the patients and their parents. One patient was excluded from the study as insufficient information was available. None of the twins suffered from postnatal disease apart from kernikterus.

The patient who was one of triplets was excluded from the analysis of twins and was considered separately.

The remaining 44 twins were matched by age of mother at delivery, social class of father and birth order with 44 control twins. The controls were extracted from a series of hospital born twins studied by Drillien (1958).

The ages of the cerebral palsied twins ranged from 18 months to 30 years at the time of the study, whereas the ages of the control twins varied only between 5 and 7 years. Of the cerebral palsied twins 70% were born in hospital compared to 100% of the control group.

The distribution of maternal age at delivery of the cerebral palsied twins was found to be similar to that of mothers giving birth to twins in an Edinburgh maternity hospital in 1955 (Table 1).

As seen from Table 2, the distribution of the cerebral palsied twins, by social class of father, showed a slight excess of twins in social classes IV and V, at the expense of III, when compared to the distribution of fathers of all live births in Scotland

TABLE 1

PERCENTAGE DISTRIBUTION, BY AGE OF MOTHER AT DELIVERY, OF 44 CEREBRAL PALSIED TWINS AND 65 LIVE BORN TWINS DELIVERED IN THE SIMPSON MEMORIAL MATERNITY PAVILION IN 1955

Age of Mother at Delivery (years)	Percentage of Mothers	
	Mothers of 44 Cerebral Palsied Twins	Mothers of 65 Hospital Born Twins
< 20	0	0
20–24	18·2	23·0
25–29	36·3	31·0
30–35	27·3	29·1
Over 35	18·2	16·9

TABLE 2

PERCENTAGE DISTRIBUTION, BY SOCIAL CLASS OF FATHER, OF 44 CEREBRAL PALSIED TWINS AND OF ALL LIVE BIRTHS IN SCOTLAND IN 1951

Social Class	Percentage of Fathers of 44 Cerebral Palsied Twins	Percentage of Fathers of All Live Births in Scotland in 1951
I and II	27·3	22·8
III	31·8	45·7
IV and V	40·9	31·5

(Registrar-General for Scotland, 1951). The control twins were selected to take this factor into account.

Results

Incidence of Twinning. The incidence of twins in this series of cerebral palsied patients is 9%. As the series is preselected the prevalence of twins may not be a true reflection of the prevalence of twins in the cerebral palsied population in general. Other workers, studying unselected material have found lower proportions of twins. In a study of 349 cases of cerebral palsy, Asher and Schonell (1950) found that 5·4% were one of twins. Illingworth (1958), reviewing 205 natal and prenatal cases found that 7·5% were one of twins. In an extensive survey of cerebral palsy in Denmark, 161 out of 2,389 patients (6·7%) were one of twins or triplets (Hansen, 1960). In a regional survey in Edinburgh, the incidence of twins among 160 children with cerebral palsy of prenatal or natal origin was 4·4% (Balf and Ingram, 1955). Shyh-Jong Yue (1955), reviewing a selected series of 301 cases of cerebral palsy found that 27 (9%) were one of twins or triplets.

Distribution of Twins According to Type of Cerebral Palsy. The 488 cases from which the twins were selected were classified according to the type of palsy. The proportion of twins in each type was then calculated (Table 3). The term diplegia refers to a more or less symmetrical paresis of cerebral origin, more severe in the lower limbs than the upper. It includes paraplegia, triplegia and tetraplegia (Balf and Ingram, 1955).

The highest incidence of twins (12·3%) was found in the diplegic group. When the diplegic patients were divided into mature and premature (by birth weight) it was found that the incidence of twins among the premature patients was 23·4% (25 in 107), while among the mature patients it was only 1·8% (two in 112). This difference is highly significant statistically ($p < 0·001$). Asher and Schonell (1950), studying unselected material, also found that twins were more prevalent among diplegic patients than in any other type of cerebral palsy.

Fate of the Other Twin. The fate of the other twin was studied in both the cerebral palsied and control groups. A twin was considered to be healthy if he had no physical abnormality and an I.Q. of 80 or over. As seen from Table 4, less than half the twins of the cerebral palsied patients were surviving and healthy. Nearly 23% of them died neonatally (as compared to 6·8% in the control group). In six pairs, one of the members died *in utero* and was delivered as a macerated foetus. In two pairs one of the twins was stillborn.

TABLE 3

DISTRIBUTION OF TWINS ACCORDING TO TYPE OF CEREBRAL PALSY

Type of Palsy	Total Number of Cerebral Palsied Patients*	Number of Twins	Percentage of Twins
Diplegia ..	219	27	12·3
Hemiplegia ..	107	7	6·5
Athetoid ..	89	8	9·0
Other	73	2	2·7
Total ..	488	44	9·0

* Including those with congenital and acquired cerebral palsy.

TABLE 4

FATE OF OTHER TWIN IN CEREBRAL PALSIED AND CONTROL GROUPS

Fate of Other Twin	Cerebral Palsied Group		Control Group	
	No.	%	No.	%
Surviving and healthy ..	20	45·5	35	79·6
Surviving, but mentally or physically abnormal ..	4	9·1	2	4·5
Died neonatally	10	22·7	3	6·8
Died between 1 month and 1 year of age	2	4·5	3	6·8
Stillborn	2	4·5	1	2·3
Macerated foetus	6	13·7	0	0

Autopsy Findings in Non-surviving Twins. Unfortunately autopsy reports were available on only two of the non-surviving twins. The death of the majority of the non-survivors was attributed to prematurity. The two infants on whom autopsy was performed showed no congenital neurological defects. One infant was found to have a congenital oesophageal atresia and the other died of intracranial haemorrhage.

One of the cerebral palsied twins died at the age of 7 years, after a dental extraction. This child suffered from severe quadriplegia with mental defect, and was one of binovular twins. Her twin died neonatally of bronchopneumonia, but no neuropathological examination was carried out. The brain of the cerebral palsied twin, however, was examined and was found to be larger than normal with an extensive developmental cleft through the right hemisphere, extending into the lateral ventricle.

Distribution of Like-sexed and Unlike-sexed Pairs. Of the cerebral palsied twins 23 were male

and 21 were female. In the control group there were 19 males and 25 females.

In the general population, the proportion of dizygotic to monozygotic twins is 2·3:1 (Smith and Penrose, 1955). On this basis and assuming that among the dizygotic twins there are equal numbers of like- and unlike-sexed pairs, the expected ratio of like-sexed to unlike-sexed twins is 1·9:1.

In the cerebral palsied group (when the twins whose partner was a macerated foetus are excluded) 27 pairs were of the same sex and 11 were of unlike sex. The excess of like-sexed over unlike-sexed twins was greater than would be expected in the group in which the other member was stillborn, died in early infancy or survived but was abnormal (15 like-sexed to three unlike-sexed pairs). There was a slight preponderance of female pairs among the like-sexed twins. When the other member of the pair was a healthy survivor, the ratio was 12 like-sexed to eight unlike-sexed pairs. Although the numbers are too small to be statistically significant ($p > 0{\cdot}05$), these findings do suggest that the chances of a like-sexed partner of a cerebral palsied twin being a healthy survivor are considerably less than those of an unlike-sexed partner.

Birth Order. In considering the birth order of the twins, the six pairs in which one member was a macerated foetus were excluded. Of the remaining 38 twins, 24 (63%) were first born and 14 (36%) second born. This difference is statistically significant ($p < 0{\cdot}05$). A preponderance of first-born cerebral palsied twins was also found by Shyh-Jong Yue (1955) and Hansen (1960).

When the entire group of cerebral palsied patients and their twins is divided according to birth order, it was found that of the stillborn and dead twins a greater proportion were second born than were first born (Fig. 1).

When cerebral palsy alone is considered, the first-born twin appears to be at a disadvantage, but when twins who suffered a worse fate are considered the prospects of the second born are considerably poorer than those of the first.

The second born of twins is exposed to a certain degree of extra risk on account of the placental separation which is liable to occur before the child is born (Baird, 1957). The finding that cerebral palsied twins are predominantly first born and the non-survivors predominantly second born suggests that the anoxia suffered by the second born of twins tends to have an immediately lethal effect rather than that resulting in survival with permanent disability. It is possible that in some of the twin pairs both members are abnormal prenatally. The

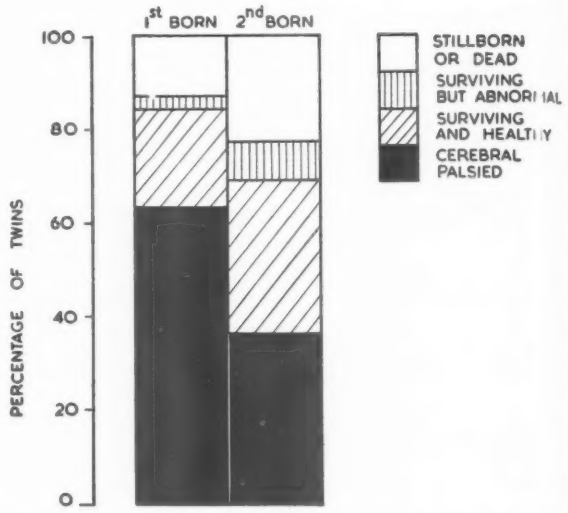

FIG. 1.—Birth order of cerebral palsied patients and their twins.

disadvantage suffered by the second born, in these cases, is additional to existing foetal abnormality and may result in a fatal outcome.

In a study of mentally-defective twins, Berg and Kirman (1960), found that second-born twins tended to be at a disadvantage both as regards mental defect and early death (including stillbirths). Yerushalmy and Sheerar (1940) found that second-born twins were stillborn more often than first-born. They did not, however, find a relation between birth order and neonatal deaths.

Birth Weight and Incidence of Prematurity. The birth weights of the cerebral palsied patients were compared to:

(1) Their surviving healthy twins;
(2) Their twins who were stillborn or died within the first year of life.
(3) Their twins who survived but were abnormal;
(4) The twins in the control group.

The six pairs in which one member of the pair was a macerated foetus were excluded from this analysis as there were no comparable twins in the series from which the controls were selected.

The average birth weight of the remaining 38 cerebral palsied twins was 4 lb. 3 oz., as compared with 5 lb. 5 oz. for twins in the control group. The average birth weight of the 20 surviving healthy twins was 4 lb. 13 oz., while that of the 14 stillborn and dead twins was only 3 lb. 8 oz. The four surviving twins who were abnormal had an average birth weight of 4 lb. 2 oz. The distribution of these birth weights is shown in Fig. 2 and Table 5.

TABLE 5

BIRTH WEIGHT DISTRIBUTION OF 44 CEREBRAL PALSIED TWINS, 20 SURVIVING AND HEALTHY MEMBERS OF PAIRS, 14 STILLBORN AND DEAD MEMBERS OF PAIRS AND 44 CONTROL TWINS*

Birth Weight (lb.)	Percentage of 44 Cerebral Palsied Twins	Percentage of 20 Surviving Healthy Twins	Percentage of 14 Stillborn and Dead Twins	Percentage of 44 Control Twins
1½–3½	30	9·5	61·6	11·4
3½–5½	46·5	61·9	38·4	43·2
> 5½	23·5	28·6	0	45·4

* The birth weights of the four surviving but abnormal members of pairs are not given.

In the 20 twin pairs in which one member was cerebral palsied and the other was normal, the individual birth weights of all but four of the healthy members were greater than those of their cerebral palsied twins.

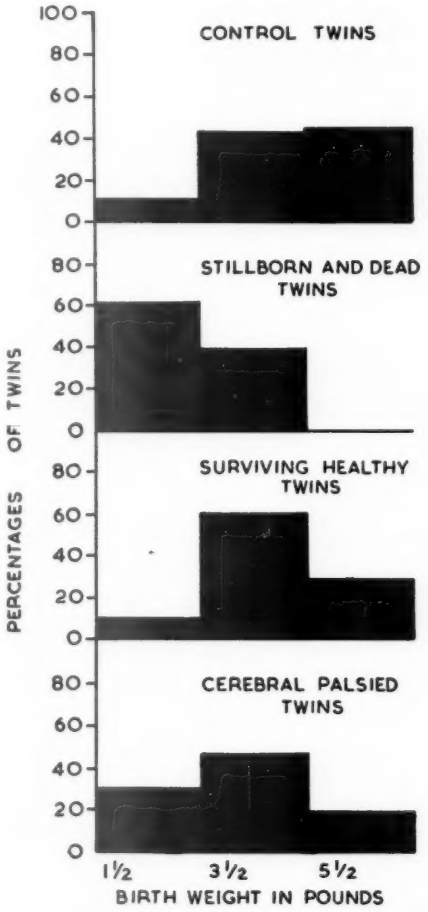

FIG. 1.—Comparison of birth weight distribution of cerebral palsied patients with that of surviving healthy twins, stillborn and dead twins, and control twins.

If a birth weight of 5½ lb. or less is accepted as the criterion of prematurity, it is seen from Table 5 that 77% of the cerebral palsied twins were premature compared to 54% of the control twins. Of the surviving healthy twins, 71% were premature compared to 100% of the non-survivors. The incidence of prematurity by weight in the general population is between 7 and 8% of all live births (Douglas, 1950).

Length of Gestation. The gestational times of the cerebral palsied twins, when known, were compared to those of the controls. As would be expected from the lower birth weights of the cerebral palsied patients, the twins in the control group were considerably more mature (Table 6). Of the control twins 45% had an estimated period of gestation of over 38 weeks, compared with only 16·2% of the cerebral palsied twins.

Abnormalities of Pregnancy. Of the cerebral palsied twins, 43% (19 of 44) were born after an abnormal pregnancy, compared to 36% (16 of 44) in the control group, a difference which is not statistically significant (Table 7). Uterine bleeding, however, was commoner in the cerebral palsied group, occurring in 10 cases. In one of these, the haemorrhage occurred during the first three months of pregnancy, in another, haemorrhage occurred

TABLE 6

LENGTH OF GESTATION OF 37 CEREBRAL PALSIED TWINS AND 44 CONTROL TWINS

Length of Gestation* (wks)	Cerebral Palsied Twins		Control Twins	
	No.	%	No.	%
< 30	1	2·7	1	2·3
30–34	18	48·7	7	15·9
35–38	12	32·4	16	36·4
> 38	6	16·2	20	45·4

* Calculated from date of last menstrual period.

TABLE 7

ABNORMALITIES OF PREGNANCIES RESULTING IN CEREBRAL PALSIED AND CONTROL TWINS

Abnormality	Cerebral Palsied Twins (44)	Control Twins (44)
Threatened abortion	1	0
Antepartum haemorrhage ..	9	1
Viral infections in first six months	2	0
Moderate or severe pre-eclamptic toxaemia	6	7
Unrelated medical conditions ..	0	4
Severe hyperemesis	0	1
Hydramnios	1	3
Total	19 or 43·2%	16 or 36·4%

TABLE 8

ABNORMALITIES OF DELIVERY OF CEREBRAL PALSIED TWINS, SURVIVING HEALTHY TWINS, STILLBORN OR DEAD TWINS AND CONTROL TWINS

Mode of Delivery	Cerebral Palsied Twins (44)	Surviving Healthy Twins (20)	Stillborn and Dead Twins (14)	Control Twins (44)
Spontaneous breech	9	3	4	1
Assisted breech ..	7	2	0	19
Forceps	2	0	1	2
Prolonged labour ..	2	2	0	0
Caesarean section ..	2	0	0	3
Face presentation ..	1	0	0	0
Spontaneous vertex delivery	21	13	9	19
Total with an abnormal delivery ..	23 or 52·3%	7 or 35%	5 or 55·5%	25 or 56·8%

both in early and late pregnancy, and in the remaining eight, the haemorrhage was after the 28th week, giving an incidence of antepartum haemorrhage of 24·5%.

In the control group, uterine haemorrhage during pregnancy occurred in only one case.

In the nine cases of antepartum haemorrhage, the other twin was healthy in five instances, died neonatally in two, was a macerated foetus in one and survived but was mentally handicapped in one. Two of the pregnancies in which antepartum haemorrhage occurred resulted in monozygotic twins, the non-cerebral palsied member of the pair being a healthy survivor in one case and mentally handicapped in the other.

Abnormalities of Parturition. Abnormalities of parturition were noted for the cerebral palsied twins, the 20 surviving members of pairs and the 14 stillborn or dead members and the control twins. As seen from Table 8, the cerebral palsied twins showed no greater incidence of abnormal parturition than the control twins. The difference in the incidence of abnormal delivery between the healthy survivors and the non-survivors was also not significant. The frequency of breech delivery was high in all groups, a finding presumably related to the high proportion of premature deliveries and the presence of a multiple pregnancy. Breech presentation, which usually occurs in only 3-4% of all pregnancies, is associated with an increased risk of mortality (Baird, 1957).

In this study, however, abnormalities of pregnancy and delivery, with the exception of uterine bleeding, were as frequent among the control twins as among the cerebral palsied.

Neonatal Course. The proportion of cerebral palsied patients, their surviving healthy twins, and the control twins showing abnormal neonatal signs was noted (Table 9). The following neonatal signs were considered abnormal: delay in initiating respiration, signs of shock, cyanotic episodes, refusal to suck and severe jaundice.

In the cerebral palsied group 68% of the patients showed abnormal neonatal signs compared to 18% of their surviving healthy twins and 13% of the control twins. These differences are highly significant statistically ($p < 0{\cdot}001$).

Five of the cerebral palsied twins showed abnormal neonatal signs after a completely normal pregnancy and delivery. In two of these, the signs were those of cerebral irritation. None of the control twins, born after an uncomplicated pregnancy and delivery, showed abnormal signs neonatally.

Signs of kernikterus were shown by four cerebral palsied twins, all dizygotic, who subsequently developed athetosis. In three of these Rh incompatibility was demonstrated. The other members of three of the pairs were healthy survivors and were not jaundiced neonatally. In the remaining pair, both twins showed signs of kernikterus and Rh incompatibility was demonstrated. The non-cerebral palsied twin died after exchange transfusion.

Ovularity. Of the cerebral palsied twins, 10 were members of probable uniovular pairs (including both cerebral palsied members of one pair) and 25 were members of probable binovular pairs. The ovularity of the remaining twins is uncertain. In only one of the nine uniovular pairs (11%) was the other member of the pair a healthy survivor as compared with 18 members of the 25 binovular pairs (72%). The advantage of binovularity over uniovularity was shown in a study of stillbirth and neonatal mortality rates of twins by Yerushalmy and Sheerar (1940). They found that the rates for uniovular twins were higher than those for binovular twins, the excess being accounted for by the larger proportion of uniovular twins in which both members of the pair died. Except in the three cases described below the criteria for monozygosity were first, evidence of a single placenta (as described in the maternity hospital records) and second, similarity of appearance when both twins survived.

TABLE 9

PROPORTION OF CEREBRAL PALSIED PATIENTS SHOWING ABNORMAL NEONATAL SIGNS COMPARED TO THEIR SURVIVING HEALTHY TWINS AND THE CONTROL TWINS

Cerebral Palsied Twins (44)		Surviving Healthy Twins (20)		Control Twins (44)	
No.	%	No.	%	No.	%
30	68·2	4	21·2	6	13·6

In four of the 10 uniovular pairs, the other member of the pair was surviving (one was normal, two were mentally retarded and both members of one pair were cerebral palsied). Blood groups of the patients and their twins were ascertained in three of these cases to substantiate the evidence of monozygosity. The twins in the remaining pair were both in homes for mentally handicapped children and blood grouping was not carried out.

Details of Three Cases of Uniovular Twins

Case 1. M.R. and W.R. are probable uniovular male twins, born in hospital after an uneventful first pregnancy lasting 34 weeks. M.R., the first born, was delivered spontaneously by the vertex, while W.R. was a spontaneous breech delivery. Their birth weights were 5 lb. 5 oz. and 4 lb. 12 oz. respectively. There was a single placenta. The neonatal period was uneventful. Both twins have paraplegia of moderate severity and in addition W.R. has a pes cavus. The I.Q. of M.R. is 49 and that of W.R. is 63. Their facial appearance and body build are very similar except that M.R. is 1 in. taller than his twin. The Rh genotypes, ABO and MN blood group systems are identical.

The identical involvement of the paresis in these twins, although their birth histories differ, suggests that natal abnormalities are not responsible for the cerebral defects. The cerebral palsy may be related to the prematurity, but the striking similarity of the disabilities of these twins suggests a genetic condition, even in the absence of a positive family history.

Case 2. W.H. and G.H. are probable uniovular female twins, W.H. being cerebral palsied and G.H. being normal. The twins were born in hospital one month prematurely after a pregnancy complicated by pre-eclamptic toxaemia. A severe antepartum haemorrhage due to placenta praevia occurred 24 hours before delivery and labour was induced surgically. Both twins were delivered spontaneously by the vertex. The affected twin, born second, weighed 5 lb. and the healthy twin, 5 lb. 4 oz. There was a single large placenta, single chorion and double amnion. The condition of both twins immediately after birth was stated to be poor after which the condition of the unaffected twin became satisfactory. The cerebral palsied twin, however, had cyanotic attacks during the first few days and fed poorly during the entire neonatal period. The affected twin suffers from severe paraplegia and is mentally retarded (I.Q. 72). The unaffected twin is a trained nurse with above average intelligence. The twins have similar facial features, skin, hair, and eye colour. The healthy twin is, however, three inches taller than her sister. The Rh genotypes, ABO and MN blood group systems are identical.

In this case it is possible that uterine haemorrhage caused separation of only part of the placenta with resultant anoxia in only one foetus.

Case 3. J.B. and K.B. are probable uniovular male twins, the former cerebral palsied and mentally retarded and the latter physically healthy, but also mentally retarded. A severe antepartum haemorrhage, due to Grade III placenta praevia, occurred just before delivery because of which caesarean section was carried out. There was a single placenta. The condition of both babies immediately after birth was stated to be poor. J.B. weighed 5 lb. at birth and K.B. weighed 3 lb. 11 oz. The twins look extremely alike. Both twins are mentally retarded. The Rh genotypes, ABO and MN blood group systems are identical.

The principal disability in these twins is their mental retardation. Unlike the two previous cases it seems probable that natal and perinatal factors were important in causing cerebral damage, the involvement being more extensive in the cerebral palsied twin than in his brother.

Triplets. One of the cerebral palsied patients (excluded from the analysis of twins) was the sole survivor of triplets. The patient, a female, suffers from severe diplegia and is mentally retarded. She was the second born of triplets and was delivered spontaneously by the vertex after a toxaemic pregnancy. The remaining two triplets, both female, were stillborn. They were delivered spontaneously, but their presentation is uncertain as is the ovularity. The cerebral palsied triplet weighed 1 lb. 8 oz. at birth. The birth weights of the remaining triplets is not known. They were, however, stated to be very small. It is probable that extreme prematurity in this case was responsible for the death of two of the triplets and extensive cerebral damage in the survivor.

Mothers' Reproductive Histories. Eight of the 44 mothers of cerebral palsied twins had had a previous or subsequent pregnancy ending in abortion or stillbirth. Seven of the 44 mothers in the control group gave a similar history. The number of siblings who were mentally defective, suffered from or died of a congenital abnormality numbered four in the cerebral palsied group as opposed to three in the control group.

Clinical Findings

INTELLIGENCE. Cerebral palsied children who are seen at the clinic are examined by a medical psychologist and an assessment of their intelligence is made. Intelligence test scores were also available

TABLE 10
INTELLIGENCE QUOTIENTS OF CEREBRAL PALSIED TWINS AND CONTROL TWINS

Intelligence Quotients	Cerebral Palsied Twins (44)		Control Twins (44)	
	No.	%	No.	%
80 or over	19	43·2	42	95·5
60–80	11	25·0	—	—
< 60	14	31·8	2	4·5

for the control twins. As seen from Table 10, all but two of the control twins had an estimated I.Q. of 80 or over, compared with only 19 (43%) of the cerebral palsied twins. The remaining two control twins and 14 of the 44 (32%) cerebral palsied twins were considered severely mentally handicapped with I.Q.s less than 60.

VISUAL AND AUDITORY DEFECTS. Visual defects were present in 16 (36%) of the cerebral palsied twins and in only two of the controls. A quarter of the cerebral palsied twins suffered from strabismus. None of the controls and 9% of the cerebral palsied twins had difficulty in hearing.

SPEECH. Speech defects were present in 27 (61%) of the cerebral palsied patients, eight of whom had no speech at all. In the control group, 11% of the twins had defective speech.

EPILEPSY. Nine (20%) of the cerebral palsied patients suffered from epilepsy. Six of these had surviving twins, only one of whom is epileptic.

Discussion

In a study of the association between complications of pregnancy and cerebral palsy, Lilienfeld and Pasamanick (1955) suggested a 'continuum of reproductive wastage' with a lethal component consisting of abortions, stillbirths and neonatal deaths, and a sublethal component consisting of cerebral palsy and related conditions. A similar concept can be applied to the birth weight distribution of cerebral palsied patients and their twins. There is a lethal component associated with very low birth weights and consisting of stillbirths and neonatal deaths, and a sublethal component associated with intermediate birth weights and consisting of cerebral palsy. The majority of twins weighing over 5½ lb. at birth are healthy survivors.

In comparing members of twin pairs it is interesting to speculate what aetiological factors could affect one twin and spare the other in so many cases. To a large extent the differences can be attributed to differences in birth weight only, but other factors should be considered.

Although the overall incidence of abnormalities of pregnancy was no greater in the cerebral palsied group than in the control group, the incidence of uterine haemorrhage was considerably higher, occurring in nearly a quarter of the pregnancies resulting in cerebral palsied children. An association between uterine bleeding during pregnancy and the production of cerebral palsy has been shown by Latham, Anderson and Eastman (1954). Antepartum haemorrhage may precipitate premature birth or may result in placental insufficiency with subsequent foetal anoxia. It is possible that this could affect one twin more than the other.

Abnormal parturition, which was as frequent in the control group as in the cerebral palsied group, does not appear to be an important aetiological factor in the production of cerebral palsy in twins.

In a previous study (Ingram and Russell, 1961) of the reproductive histories of mothers of children suffering from congenital diplegia, it was found that a high proportion of the pregnancies of these mothers ended in abortion, stillbirth, neonatal death or malformed children. The mothers also tended to be older at delivery than expected. Although the numbers in the present study are small, they suggest that mothers of cerebral palsied twins do not have any more unsuccessful pregnancies and are not any older at the time of delivery than would be expected.

The most important aetiological factor in the production of cerebral palsy in twins appears to be immaturity as indicated by low birth weight. The birth weights of the cerebral palsied twins and their estimated maturity were considerably less than those of the control twins. Two explanations are suggested for these findings. It may be that among children who are prematurely born as a result of a multiple pregnancy, those who are smallest and least mature have the greatest tendency to develop cerebral palsy. It has been established that prematurity predisposes to intracranial injury (Craig, 1938; Parsons, 1944) and that the lower the birth weight and the less the maturity the higher is the mortality (Benda, 1945; Crosse, 1957). Premature infants are also more liable to suffer complications in the neonatal period, leading to subsequent physical and mental handicap. The excess of cerebral palsied over control twins showing abnormal neonatal signs may be related to their lower average birth weights. The prevalence of twins among diplegic patients is due almost entirely to prematurely born twins. Among maturely born diplegic patients only two of 112 patients were one of twins. As the incidence of prematurity among

diplegic patients (over 40%) is higher than in any other type of cerebral palsy, it is probable that prematurity alone is responsible for the high incidence of twins in this group. Plural pregnancy in itself carries greater risks to the foetus than a single pregnancy (Baird, 1957). It may be that the high incidence of cerebral palsy in twins is due entirely to the combination of prematurity and multiple pregnancy which heavily predisposes the infant to cerebral damage.

However, as multiple pregnancy is common to both the cerebral palsied and the control twins, it can be postulated that the greater degree of prematurity of the cerebral palsied twins is due to additional and adverse factors acting *in utero*. A prenatally injured foetus tends to be prematurely born. This concept was originally suggested by Freud (1897) and supported by Collier (1899, 1923) to explain the relationship between Little's disease and premature birth. More recently it has been shown that infants with congenital malformations tend to be born prematurely (Murphy, 1940). It is possible that an unfavourable intrauterine environment results in cerebral damage to one or both products of the multiple pregnancy. Even in a monozygotic twin pregnancy, the intrauterine environment may not be identical (Price, 1950), and factors acting adversely on one foetus may spare the other. Pre-existing foetal abnormality partly accounts for the finding that neonatal abnormalities, but not abnormalities of parturition, are considerably higher among the cerebral palsied twins than among the controls. An infant with a congenital cerebral defect may show neonatal signs similar to those shown by a birth injured foetus.

The high casualty rates and low birth weights of the other members of the twin pairs substantiate either of the above explanations. An extensive neuropathological study of non-surviving members of twin pairs would be of value in elucidating the problem further.

Summary

Forty-four pairs of twins are described in which one member of each pair suffers from cerebral palsy. They are compared with 44 control twin pairs.

Incidence of Twinning. The 44 cerebral palsied twins were extracted from 488 consecutive cases of cerebral palsy, giving an incidence of twinning of 9% the highest incidence being among diplegic patients.

Fate of the Other Twin. Less than half of the twins of cerebral palsied patients were surviving and healthy. The majority were stillborn (including those delivered as macerated foetuses), died neonatally or within the first year of life or were mentally handicapped.

Sex Distribution. The ratio of like-sexed to unlike-sexed pairs was greater than would be expected in pairs in which one member was cerebral palsied and the other was stillborn or had died in early infancy.

Birth Order. There was an excess of first-born cerebral palsied twins and second-born stillborn or dead twins.

Birth Weight. The average birth weight of the cerebral palsied patients was less than that of their surviving healthy twins and of the control twins. The stillborn or dead twins had the lowest average birth weight of all groups and were all premature.

Maturity. The maturity of the cerebral palsied twins, based on the estimated period of gestation, was considerably less than that of the control twins.

Pregnancy and Parturition. The incidence of abnormal pregnancy and parturition was no greater in the cerebral palsied group than in the control group. The ages of the mothers at the time of delivery were no greater than expected.

Neonatal Course. The cerebral palsied patients showed more abnormal neonatal signs than did their surviving twins and the control twins.

Ovularity. The casualty rate among the nine pairs of probable uniovular twins was higher than that among the 25 pairs of probable binovular twins. Three pairs of uniovular twins in which both members survived are described.

Clinical Findings. The incidence of mental impairment, visual, auditory and speech defects was considerably higher among the cerebral palsied twins than among the controls.

Conclusion. In the majority of cerebral palsied twins the cerebral defect is unrelated to abnormalities of pregnancy and parturition or to maternal age. The most important factor appears to be low birth weight due either to multiple pregnancy alone, or to a combination of multiple pregnancy and pre-existing foetal abnormality.

I am indebted to Dr. C. M. Drillien for permission to use case histories of 100 pairs of twins and also for her helpful suggestions. I am grateful to Dr. T. T. S. Ingram for his encouragement and advice during the preparation of the paper, and to Professor R. W. B. Ellis for his helpful criticism. I wish to thank the Scottish Council for the Care of Spastics for providing facilities for research.

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EPIDERMOLYSIS BULLOSA HEREDITARIA LETALIS

BY

T. G. MADDISON and R. A. BARTER

From the Royal Women's Hospital, Melbourne

(RECEIVED FOR PUBLICATION SEPTEMBER 30, 1960)

Epidermolysis bullosa is a rare chronic hereditary skin disorder characterized by the formation of vesicles and bullae which develop spontaneously or as a result of slight trauma. Although several varieties have been described, there are three main clinical types.

The simple non-scarring type appears in infancy or childhood in otherwise normal children. The bullae develop mainly over parts exposed to trauma, such as the hands and feet. There is no involvement of the mucous membranes or nails. It is dominant in inheritance.

The dystrophic type is more severe and appears at, or soon after birth. Scarring usually follows and the mucous membranes are involved together with deformity and loss of finger and toe nails. Both recessive and dominant inheritance sub-types have been described.

The third type, epidermolysis bullosa hereditaria letalis, was first described by Herlitz (1935). The bullae appear at birth or soon after. They are extensive and progressive, but some may heal without scarring. The mucous membranes are involved and the nails may be lost or deformed. This type is recessive in inheritance, and death usually occurs within a few months.

The clinical features of epidermolysis bullosa hereditaria letalis have been reviewed in articles (Davidson, 1940; Leland and Hirschl, 1954; Lewis, Steven and Farquhar, 1955; Silver, 1957). Silver stated that 46 cases had been reported, and added a further case showing all the features of the disease except the usual fatal outcome, the child being alive at 30 months.

It is the purpose of this paper to present two further fatal cases of the disease, and to describe additional pathological features indicating a more widespread epithelial disorder.

Case Reports

Case 1. M.H., a girl, was delivered prematurely, weighing 1,820 g., following a mild accidental haemorrhage in a twin pregnancy on January 16, 1957, at the Royal Women's Hospital. The other twin, a boy, weighing 2,550 g., was normal. The mother had one normal child aged 18 months. The family history was normal.

Immediately after birth there were raw red areas on the back of both feet and ankles, and around the wrist. Strands of mucous membrane were hanging from the mouth.

On the next day, bullae developed on the buttocks, the fingers of the left hand and the back of the right hand (Fig. 1). The skin could be removed by light pressure (Nikolsky's sign). The nails of two toes on the left foot, and one on the right, separated over the next few days.

She was given A.C.T.H. gel 20 mg. daily for four days from January 17, without any influence on the developing bullae. A solution of penicillin and streptomycin sprayed on the lesions produced better drying and healing than vaseline gauze dressings. Despite parenteral antibiotics, the skin lesions became infected with

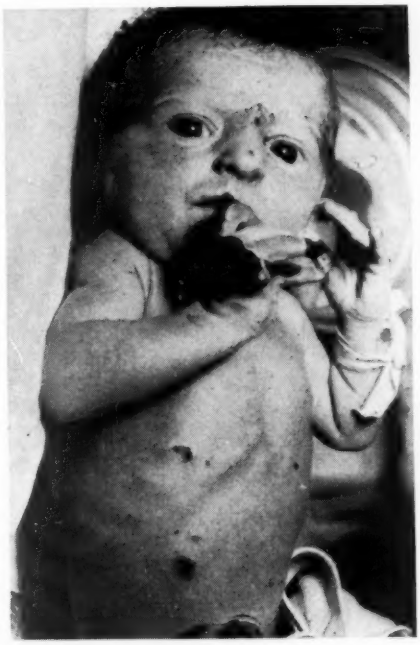

FIG. 1.—Case 1: showing extensive ulceration of the back of the right hand and fingers and small lesions on the trunk.

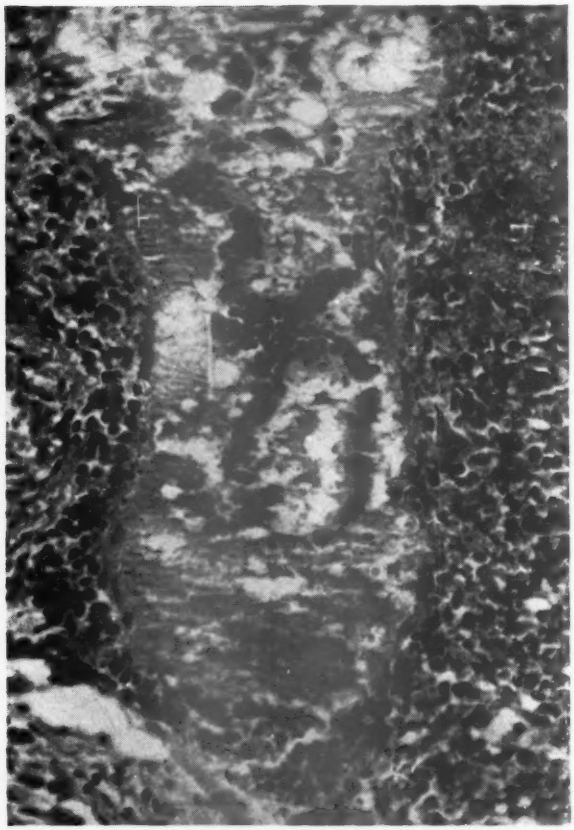

FIG. 2.—Case 1: showing lifting of the epithelial lining of a bronchiole by fluid. This lesion is essentially the same as that seen in the skin. (H. and E. ×83.)

Staphylococcus aureus. The infant's condition gradually deteriorated, she became moderately jaundiced, further skin lesions developed, and she died nine days after birth.

Autopsy Findings

MACROSCOPIC. Autopsy was performed four days after death. The body was kept in a refrigerator at 4° C.

Large areas of skin were ulcerated. One ulcer on the left side of the chest measured 6 cm. in diameter. There were other areas of ulceration around the mouth, on both sides of the nose, on the elbows, hands, feet, buttocks and lower part of the back. In the left thalamus there was an area of icteric staining 4 mm. in diameter. The aortic intima showed marked jaundice. Both lungs contained a moderate amount of air. The right upper lobe was congested and solid. Patchy areas of congestion were seen in the left lower lobe. The trachea and main bronchi were congested and contained a large amount of tenacious mucus. The thyroid was smaller than normal. The material in the intestine was partly clay coloured and partly brown. The gall bladder was distended and contained colourless fluid. The liver was of normal size, and had sharp edges. The other organs appeared normal.

MICROSCOPIC

Lungs: Some alveoli contained oedema fluid and there were patchy interstitial inflammatory infiltrations. In a few there were fibrin and occasional red cells. The alveolar capillaries were intensely congested. Masses of bacteria were seen throughout the lungs. Some bronchi and bronchioles had an intact columnar epithelial lining. In others this lining was lifted from the lamina propria by fluid (Fig. 2). However, most bronchioles and an occasional small bronchus had no epithelial lining. They were filled by masses of degenerate columnar epithelial cells mixed with amorphous material.

Trachea: The epithelial lining appeared normal. There was no separation from the lamina propria by fluid.

Skin: At the site of a bullous lesion the epidermis was lifted from the underlying tissues and bacteria were seen. There was some haemorrhage in the dermis immediately beneath the area where the epithelium had lifted and very little inflammatory cellular infiltration was seen.

Liver: Small plugs of bile were seen in and between the parenchymal cells, and there was moderate congestion of the sinusoids.

Pancreas: Eosinophil leucocytes were conspicuous in the interstitial tissues.

Suprarenals: There was marked congestion of the medulla and the inner half of the cortex. Haemorrhages were present in the fibrous tissue behind the gland.

Kidney: Haemorrhages were present around the pelvis. The heart, thyroid and spleen showed no significant abnormality.

Case 2. J.L., a girl weighing 3,685 g. was delivered spontaneously at term on February 19, 1957, at the Royal Women's Hospital. The mother had a normal child aged 6 years. The family history was normal.

At birth, the infant had a blister on the chin and there was a raw area on the back of the left hand. Over the next three days large superficial bullae developed (Fig. 3), especially over the buttocks, and six finger nails commenced to separate. One week after delivery bullae were present around the umbilicus, on the back of the neck and on the shoulders. There were three small ulcers on the palate. Some bullae healed without scarring. Nikolsky's sign was positive. When aged 3 weeks she was admitted to the Royal Children's Hospital, Melbourne. Despite local treatment to the skin and parenteral chemotherapy the skin lesions became infected with *Pseudomonas pyocyanea*, the infant's condition deteriorated, further skin lesions developed and she died at the age of 5 weeks.

Autopsy Findings

MACROSCOPIC. Autopsy was performed nine hours after death by Dr. Alan Williams at the Royal Children's Hospital, Melbourne.

Large areas of ulceration covered by coagulum were present on the trunk, face and limbs. The lungs were congested. The trachea and main bronchi were inflamed and contained mucus and aspirated food. The thymus was atrophic.

FIG. 3.—Case 2: showing extensive lesions on arm, trunk, buttocks and leg.

MICROSCOPIC. The lungs showed scattered intra-alveolar haemorrhages, patchy collapse and small areas of early bronchopneumonia. Scattered inflammatory infiltrations were seen around the renal pelvis, and in the medulla and cortex of the kidney. In the skin taken from an apparently normal area, there was a complete absence of rete pegs. The basal layer consisted of cells which appeared flatter than normal and the change from the nucleated cells to those at the surface was unusually abrupt.

Discussion

These two cases of epidermolysis bullosa hereditaria letalis are described because of the rarity of the disease, and to record lesions of epithelial surfaces other than the skin. Leland and Hirschl (1954) have already described vesicular lesions in the trachea, bile ducts and pancreas, but tended to regard them as artifacts. In the first case presented here, there is direct evidence of vesicular lesions in the bronchioles and indirect evidence of involvement of the common bile duct. Consideration has been given to the possibility of post-mortem changes causing the appearances in the lungs, particularly because of the long interval between death and autopsy. There were no unusual post-mortem changes in other organs, however, and the pulmonary lesions were essentially the same as those observed in the skin. In the early lesion a clear fluid separated the columnar epithelial lining from the lamina propria in the terminal bronchioles, and in a very occasional small bronchus. With rupture of the vesicle, fluid passed downwards into the lung, and masses of degenerate epithelial cells filled bronchiolar lumina which were devoid of epithelial lining.

In this case also the presence of jaundice, mucocele of the gall bladder, bile thrombi in the liver, and clay-coloured material in parts of the bowel, indicated obstruction of the common bile duct, above the origin of the cystic duct. It is considered likely that the obstruction resulted from the presence of one or more vesicular lesions, or degenerate cellular material from such lesions, filling the lumen of the duct. No other lesions in the smaller ducts of the liver or pancreas were found microscopically.

Summary

Epidermolysis bullosa hereditaria letalis is a rare hereditary skin disorder. The skin lesions develop after birth, and eventually lead to death in infancy.

The present study indicates that bullous lesions in the skin are not the only abnormality as similar lesions have been found in bronchioles and other findings also indicate probable involvement of the extra-hepatic bile ducts.

We wish to thank Dr. John Colebatch under whose care both infants were treated, and Dr. Alan Williams for supplying details of the autopsy findings in the second case.

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NEUROFIBROMATOSIS WITH PATHOLOGICAL FRACTURES IN THE NEWBORN

BY

FLORENCE McKEOWN and MURIEL J. L. FRAZER

From the Department of Pathology, Queen's University, and City Hospital, Belfast

(RECEIVED FOR PUBLICATION JULY 29, 1960)

Neurofibromatosis may be recognized in childhood, though it is unusual for the full syndrome to be present at an early age. Thus skin pigmentation may be the only manifestation in infancy, later to be followed by the development of skin tumours, skeletal and other abnormalities.

The following case of neurofibromatosis is of interest in that it occurred in a newborn infant who presented with skin pigmentation, bowing of the legs, pathological fractures, cardiac irregularity, and enlargement of the clitoris.

Case Report

Barbara, the second child of young, unrelated parents, whose other child is healthy, was admitted to the Neonatal Sick Unit of the Jubilee Maternity Hospital, Belfast, on October 27, 1959, being then 11 days old. She was referred because of 'a patch of skin which goes white when she cries' (and she cried a great deal), but it was found that while there was indeed an irregular area over the right clavicle which did not flush with the rest of the skin, there were also *café au lait* blotches on the trunk, a patch of alopecia in the right parietal region, enlargement of the clitoris, bowing and thickening of the left leg, and reluctance to move the right arm.

Radiographs showed fractures of the left tibia and fibula and right ulna and an unusual bowing of the right tibia and fibula. The femora appeared normal. The appearances were not considered typical of Albright's disease (Figs. 1 and 2).

On October 28, the baby had a sudden, severe, cyanotic attack, with an irregular apex rate of 240 per minute. E.C.G. showed 'runs of atrial tachycardia and multiple ectopics, mainly ventricular'. The tachycardia ceased after the administration of intravenous digoxin and no further attacks were observed. The baby, however, failed to thrive.

No abnormality was found in the blood chemistry, apart from a moderately raised blood urea (84 mg. %). A few pus cells were present in a catheter sample and there was a moderate growth of coliform bacilli sensitive to streptomycin only, a course of which was given, and by November 10 the urine was clear and sterile. Despite this, however, and though no other clinical sign of infection was apparent, the temperature began to rise, and in spite of further antibiotic treatment, she died on November 23, by which time the brownish pigmentation involved almost half the surface of the trunk.

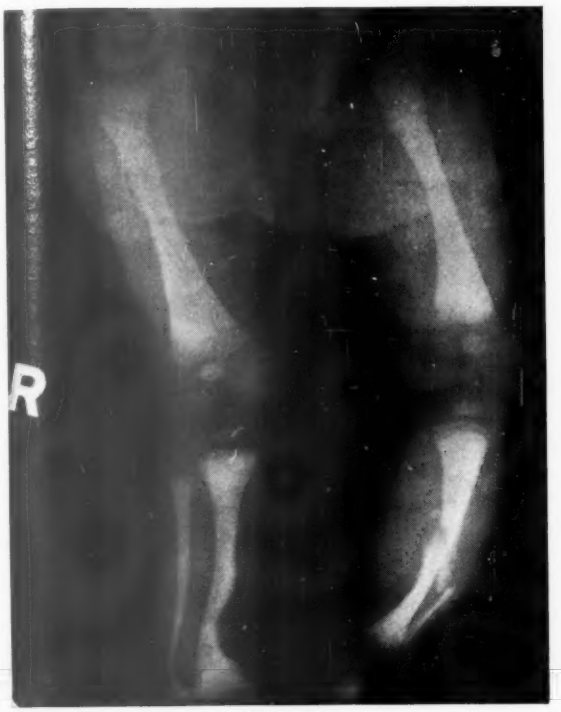
The genital abnormality was not, unfortunately, investigated fully during life; on rectal examination a normal-seeming infantile uterus was found, but in view of the multiple fractures, and, indeed, of her steady downhill course, it was not possible to collect a 24-hour specimen of urine for endocrine assay.

Post-mortem Examination. At autopsy the main external features of note were the bowing of the tibiae with fractures palpable in the lower third of the left tibia, and in the right ulna, the *café au lait* spots around the umbilicus, slight alopecia in the right parietal region, and enlargement of the clitoris. There were no skin tumours.

Macroscopically the heart and lungs showed no abnormality. The abdominal organs were quite normal and the only positive finding in the abdomen was the presence of a 1 cm. nodule of tissue related to the coeliac plexus. The cranial contents appeared normal. The tibiae and fibulae and samples of other bones were removed for histology. All organs were examined histologically, but only the relevant sections will be described.

Histology

Left tibia. In general the periosteum showed slight thickening, and the nerves related to it showed a diffuse intraneural fibrosis. There was slight osteoclastic proliferation in the underlying cortex, but on the whole the cortex was thicker than normal and the trabeculae were broad and well formed. At the site of the fracture there was much proliferation of granulation tissue and a little calcifying cartilage, but the broken ends of the bone were largely separated by a mass of neurofibromatous tissue developing in the medullary cavity, and situated along the course of a main nerve trunk which could be seen perforating the adjacent cortex. The interlacing bundles of fibrous tissue intimately mixed with nerve fibres, with more obvious Schwann cell proliferations forming Verocay bodies, identified the lesion as a neurofibroma (Fig. 3). A feature of the tumour was the presence of many large thin-walled blood vessels coursing within the affected nerves (Fig. 4). Other neurofibromatous nodules were present in the medullary cavity even



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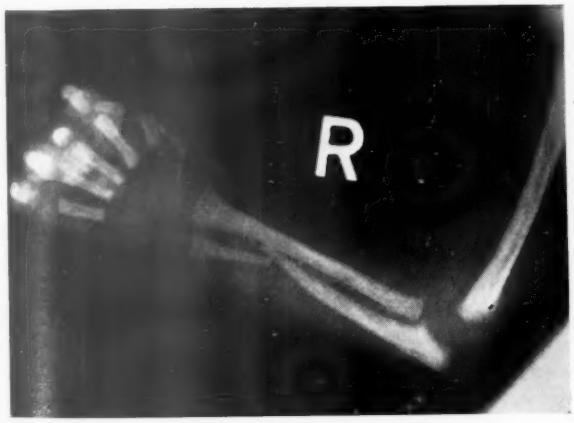

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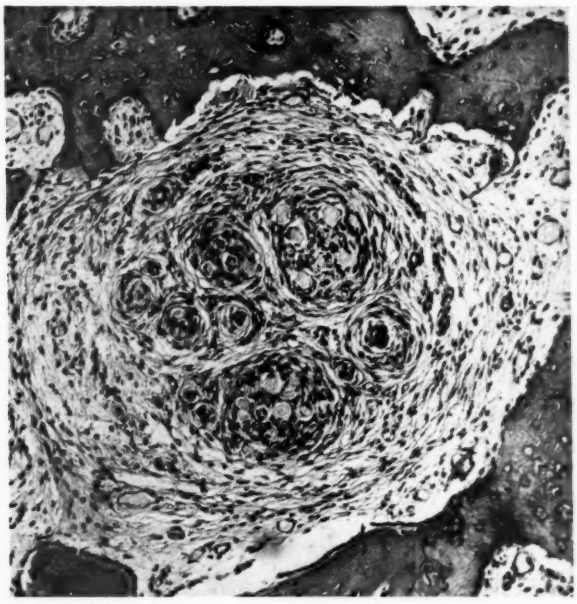

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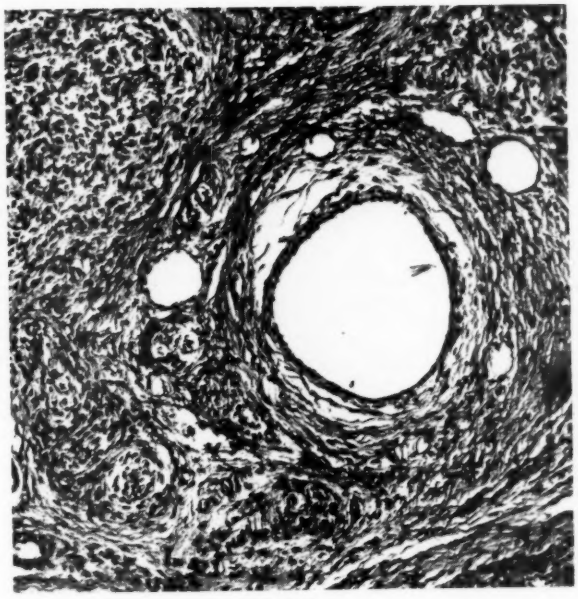

FIG. 4.

FIG. 1.—Radiograph of lower limbs showing bowing of right tibia and fibula, and fractures of left tibia and fibula.
FIG. 2.—Radiograph showing fracture of distal third of right ulna.
FIG. 3.—Section of left tibia showing intramedullary neurofibroma at level of fracture. (H. and E. × 35.)
FIG. 4.—Section of left tibia, showing the rich vascular pattern in a large intramedullary neurofibroma. (H. and E. × 85.)

at a distance from the fracture and showed the same rich vascularity.

In the right tibia, where bowing was the only macroscopic change, histological examination revealed neurofibromatosis of the periosteal and intramedullary nerves, but not to such a degree as in the fractured tibia. There was also some thickening of the cortex, with fibrosis of the marrow. Skull, pelvic bones, ribs and vertebrae showed no abnormality histologically.

Nodule from coeliac plexus. This proved to be a neurofibroma in which there was some mucoid degeneration of the fibrous tissue. There were some ganglion cells present also.

Vagi. These were examined at several levels and

throughout their intrathoracic course the nerves showed much intraneural fibrosis resulting in expansion of the trunks to about twice their normal size. There was some loss of nerve fibres, but the perineural sheath, though thickened, was not disrupted (Fig. 5). Other peripheral nerves, both visceral and skeletal, showed diffuse thickenings and clubbed expansions which were only detected on histological examination. No cause for the enlarged clitoris could be found. All endocrine organs appeared normal (though with minor abnormalities of innervation) and no lesion could be detected in the hypothalamus.

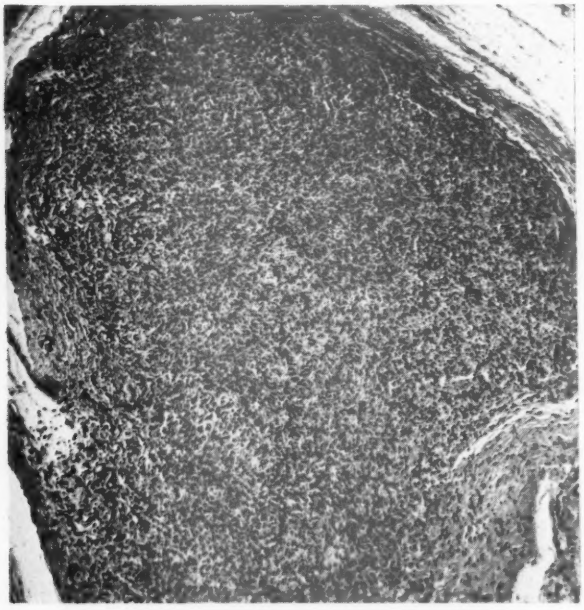

FIG. 5.—Vagus, showing neurofibromatous expansion of the nerve, and slight perineural fibrosis. (H. and E. × 35.)

Discussion

Skeletal changes in neurofibromatosis have been recognized for a considerable time and have been well documented (Brooks and Lehman, 1924; Holt and Wright, 1948; Levene, 1959). They have been reported to occur in 7% of cases, but this estimate may be on the low side as many patients with the disease have not been subjected to radiological examination.

A variety of lesions occur, the commonest being scoliosis. Little is known about the pathological basis for this lesion, but it has variously been attributed to periosteal or intraosseous neurofibromata, or compensatory to other deformities. Disorders of skeletal growth are another feature, manifesting themselves in increase in length or stunting of growth, increase in density or rarefaction of the affected bones. The third group of bony lesions includes pedunculated periosteal growths, intracortical cysts or cysts within the medullary cavity. These may lead to fracture and pseudoarthrosis. Some of these lesions have been proven to be due to neurofibromata in the affected stes, but many have been diagnosed by radiological examination only and have been presumed to be neurofibromatous. Jaffe (1945) refers to the relative infrequency with which skeletal lesions of neurofibromatosis are due to the actual presence of a neurofibroma on a bone or within its interior. It must be emphasized that without histological examination it is impossible to be certain what proportion of bony lesions are definitely neurofibromatous.

Parkes Weber (1930) attributes the other abnormalities of bone such as hyperplasia to excessive blood supply secondary to the periosteal neurofibromatosis. Vascular anomalies do occur in this disease and some of the tumours are almost angiomatous. In the present case a remarkable feature was the abnormally rich blood supply incorporated within the periosteal and intramedullary tumours and this may have been a factor in causing thickening of the cortex and bowing of the tibiae.

In addition to these relatively distinctive skeletal lesions, there is a further small group of patients with the generalized bony changes of osteomalacia and it has been suggested that these patients have an associated renal tubular defect with excessive excretion of phosphate (Swann, 1954).

Two cases of Paget's disease have also been described in association with neurofibromatosis, but Levene (1959), in recording one such case, assumes that there is no definite connexion between the two conditions.

It is evident, therefore, that a wide range of skeletal manifestations may occur, and apart from osteomalacia which is seldom observed, intramedullary neurofibromata such as occurred in this case are probably the most rarely encountered or at least histologically proven bone lesions of neurofibromatosis.

A variety of endocrine disturbances may also occur and indeed Thannhauser (1944) subdivides neurofibromatosis into cutaneous, nervous, visceral, osseous and endocrine syndromes.

Endocrine disturbances include precocious puberty, hypogonadism, myxoedema, Addison's disease, and acromegaly. Ford (1960) emphasizes that the type of acromegaly which occurs is almost always atypical, and is more likely to be due to local disease of bone than to an endocrine disorder. It was difficult to find a basis for the enlargement

of the clitoris in the present case. All endocrine organs were normal on histological examination, as was the hypothalamus. Petsche and Radlinger (1954) report a case with ovarian aplasia and external masculine pseudohermaphroditism. It is of interest that Biggart (personal communication) also recalls a case of neurofibromatosis in a female child who had a neurofibroma of the coeliac plexus associated with enlargement of the clitoris which subsided on surgical removal of the tumour. This suggests that the basis for this and possibly other endocrinopathies may occasionally be primarily neurogenic.

From the clinical point of view this case was interesting not only for the presence of fractures in the newborn, but also for the irregularity of the heart, with ventricular ectopics and runs of atrial tachycardia. This was attributable to diffuse neurofibromatosis of the vagi. Intrathoracic neurofibromata are relatively infrequent in von Recklinghausen's disease (Maksim, Henthorne and Allebach, 1939) and involvement of the vagus is very rare (Tuttle, Sanai and Harms, 1956). Gerbode and Marguiles (1953) were able to find only two reports of intrathoracic nerve sheath tumours which arose from the vagus.

Although a terminal septicaemia could not be excluded as the immediate cause of death in this patient, no doubt the cardiac dysfunction was a contributory factor.

Summary

A case of neurofibromatosis is described in an infant aged 4 weeks, presenting with skin pigmentation, pathological fractures, enlargement of the clitoris and cardiac irregularity. Extensive neurofibromatosis of peripheral nerves was found, including the vagi, together with a neurofibroma of the coeliac plexus. The fractures were related to intramedullary neurofibromata.

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FAMILIAL ATAXIA-TELANGIECTASIA

BY

J. D. PICKUP and R. J. PUGH

From the General Infirmary, Pontefract, and the Victoria Hospital for Sick Children, Hull

(RECEIVED FOR PUBLICATION AUGUST 11, 1960)

A familial syndrome of progressive cerebellar ataxia and choreoathetosis, associated with oculocutaneous telangiectasia and recurrent sinobronchitis in childhood, has recently been described in the American literature. The close similarity of the clinical features observed by Boder and Sedgwick (1957, 1958), Wells and Shy (1957), Biedmond (1957), Centerwall and Miller (1958) and Ford (1960) leave no doubt that this represents a new clinical entity to which the two brothers reported here belong. Credit for the first published description belongs to Mme. Louis-Bar (1941).

Case Reports

David and Barry are the only children of a non-consanguinous union. Their parents, who are divorced, are both in good health and the father has a normal infant daughter by a second marriage.

David. Born on February 22, 1944, and now aged 16 years, David thrived without causing anxiety during infancy. He weighed 6 lb. 6 oz. at birth. Delivery was uncomplicated by injury or anoxia and there was no neonatal jaundice. Locomotor development was at first reassuring with independent walking achieved by 13 months, but from the age of 2 years he gradually became awkward and unsteady, particularly when tired. He lurched unexpectedly, threw out his legs wildly when hurrying and developed irregular movements in the arms. About this time his parents also became aware of a periodic hesitancy in speech and both commented upon the 'blood shot' appearance of his eyes, particularly when excited. Facial grimaces, shaking of the head and drooling of saliva were all prominent by the age of 4½ years when he first attended the paediatric clinic and his demeanour then suggested athetoid cerebral palsy.

In other fields of attainment David made slow progress. He was fully continent and could feed himself by the age of 3 years and was talking in sentences a year later. At his local school he gave an impression of understanding what was required of him, but found writing increasingly difficult, and talked explosively and indistinctly. His teacher reported that he was 'intelligent', but had little control over his features or limbs. Intelligence testing with the Terman Merrill scale at the age of 8 years gave an Intelligence Quotient of 85, which on retesting three years later had fallen to 65. At 13 years David moved from his day school to a residential school for cerebral palsied children, which he has now left to begin attendance at a local occupation centre.

CLINICAL FEATURES. When first examined by one of us (J.D.P., July 2, 1952) the generalized writhing and jerking of his limbs and facial muscles resembled choreoathetosis. The slurred indistinct speech, drooling of saliva and the irrelevant screwing up of his features gave a false impression of inattention. His injected eyes on close inspection showed telangiectasia of the conjunctivae and ciliary muscles, but were otherwise normal. Walking was propulsive and unsteady, while fine movements of the hands were poorly co-ordinated and laboured. There was no nystagmus and no intention tremor on finger nose testing. The deep reflexes were present but depressed and the superficial reflexes were normal.

PROGRESS. During the ensuing seven years David has gradually deteriorated with progressive ataxia and repeated respiratory infections. By the age of 15 years he was unable to walk unaided and now requires firm support when seated to avoid slipping off a chair. The choreo-athetotic movements continue unceasingly, with writhing of the face, neck, trunk and limbs punctuated irregularly by lunging and jerking. These movements stop during sleep and are reduced by voluntary effort, but make all fine movements laborious in the extreme. David can usually dress himself completely, but he requires nearly an hour to do so, while his signature which is still legible, occupies several minutes of concentrated effort. He feeds himself, is fully continent and can move about in a self-propelling wheel chair. His speech is now too laboured to support a conversation, but remains intelligible. For several years nasal obstruction, drooling of saliva, and irregularity of respiration have been conspicuous. It seems that incoordination of swallowing and breathing contributes to his repeated episodes of lower respiratory infection.

The ocular telangiectasis remains prominent and recently cutaneous lesions including raised pigmented patches (Fig. 1), vesicles and spider naevi have appeared over the face, arm flexures and trunk.

Investigations have been generally uninformative: Blood group A, Rh positive, CDe/CDe; Wassermann and Kahn reactions negative; liver function tests normal; serum protein electrophoresis normal; urine chromatography normal; copper metabolic studies normal.

FIG. 1.—David: Close-up view, showing telangiectasia of the eyes and pigmentation of the face.

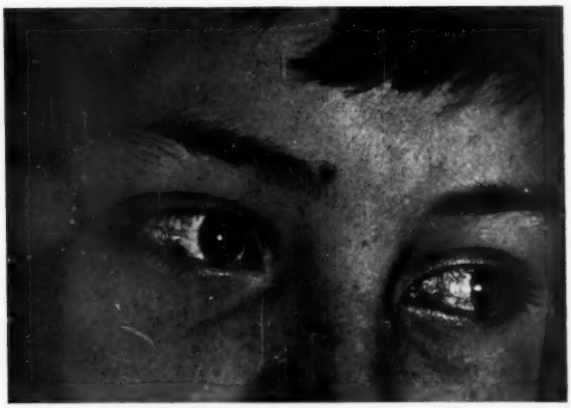

FIG. 2.—Barry: Close-up view, showing telangiectasia of the eyes and pigmentation of the face.

Barry. Born on July 15, 1948, and now aged 12 years, he was premature, weighing 5·0 lb. He thrived in early infancy and occasioned no anxiety until late in the first year when his eyes were appreciably injected. He sat at 9 months, crawled at 11 months, and was walking independently soon after 1 year of age. He began to use words at 15 months and to converse by the age of 2 years. The close resemblance to his brother was emphasized when irregularities of hand movements and gait appeared at about 3 years of age. In retrospect Barry's progress has been very similar to that of David, with gross choreoathetosis and ataxia evident by 5 years and the degree of incapacity remaining compatible with attendance at ordinary school until the 11th year. Recently Barry has been unable to play freely out of doors or to travel by public transport unaccompanied. He is awaiting admission to a residential school for cerebral palsied children.

Ophthalmological examination when 5 years old showed well-marked dilatation of the conjunctival ciliary vessels in both eyes and the underlying sclera appeared unusually transparent. His speech by then was slurred and precipitate.

An intelligence test at the age of 8 years gave an I.Q. of 85, but at the age of 10 years he could only read the simplest words and had mastered only the 2 times multiplication table. Observed alongside his brother, Barry shows the same range of involuntary movements, affecting his face and extremities in particular, but not to the same degree. In both, these movements are a combination of continuous writhing interrupted by irregular jerking. He is able to sit more erect than David, to walk unaided but with marked ataxia and with feet placed well apart, and his speech is more audible. Both their mother and maternal grandfather agree, however, that the two boys are equally severely affected, making due allowance for the differences in ages.

Neurological examination shows generalized hypotonia with depressed deep reflexes and normal abdominal and plantar responses. There is nystagmus on looking laterally and loss of balance standing when the eyes are closed. Hand movements are laboured and ataxic but without any fine intention tremor. Barry can feed, wash and dress himself and he is fully continent. Writing is achieved only with great effort. Breathing is noisy and irregular, and swallowing incoordinate, allowing saliva to ruckle in the throat and to trickle out of the mouth. He shows ocular telangiectasis and *café au lait* patches over the skin (Fig. 2), but no cutaneous telangiectasia; however, the nasal mucosa is swollen and nasal congestion always troublesome. Acute lower respiratory infections occur regularly during the winter months.

Investigations have not brought to light any abnormal clinical pathology: Blood group O, Rh positive, CDc/CDc; Wassermann and Kahn reactions negative; liver function tests normal; electrophoresis of plasma proteins normal; urine chromatography normal; a skull radiograph shows no calcification; cerebrospinal fluid examination shows no abnormality.

Discussion

The outstanding feature of this rare syndrome is the combination of conspicuous ocular telangiectasia with progressive cerebellar ataxia in early childhood. A superficial resemblance to athetoid cerebral palsy is dispelled by the progressive character of the involuntary movements and the development of a true ataxia. Cutaneous telangiectasia most commonly involving the cheeks, the nasal bridge, the external ears, the neck root and the skin over bony prominences, when fully manifest provides the very characteristic clinical picture illustrated by Centerwall and Miller (1958). *Café au lait* pigmentation of varying degree present in Mme. Louis-Bar's case was noted by Boder and Sedgwick (1957), and is evident on the face in both the children reported here.

Associated respiratory symptoms present with progressive nasal congestion and mouth breathing. Drooling is regularly troublesome and recurrent acute lower respiratory infections probably result

from the increasing incoordination of swallowing and breathing so that much naso-pharyngeal secretion is inspired.

Autopsy findings are reported by Boder and Sedgwick (1958) and Centerwall and Miller (1958) both of whom found neuronal degeneration maximal in the cerebellum and associated with enlarged venules in the cerebellar leptomeninges and in the white matter of the cerebellum.

Summary

An account is given of two brothers in whom progressive cerebellar ataxia is associated with telangiectasia of the conjunctivae and more recently of the skin. Progressively severe sinobronchitis completes the clinical entity of ataxia-telangiectasia which has only recently been described.

Acknowledgement is gratefully made to Dr. Dixon who attended David in a Bolton residential school.

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BOOK REVIEWS

Practical Dietetics. Edited by WILLIAM A. R. THOMSON. (Pp. 64. 4s. 6d.) London: The Practitioner. 1960.

This little pamphlet contains articles originally published in *The Practitioner* during the year 1959, and reprinted as a result of their success with general practitioners. It comprises 12 contributions, each by a dietitian, on a variety of medical conditions. Only two on weaning and gastroenteritis directly concern children, but some of the others, i.e. that on obesity, are also of interest to the paediatrician. They are written in the language of dietitians rather than of doctors, but nevertheless are evidently useful for hasty reference in the consulting room.

Health in Childhood. By RICHARD W. B. ELLIS. (Pp. 251; 16 figures + 16 plates. 5s.) Harmondsworth: Penguin Books. 1960.

At five shillings, the price of a cheap toy, this book, a detailed and clearly-written account of all factors relating to health in childhood, is within reach of every home and should be on every family's bookshelf.

From it, for example, the young mother will learn that play serves many purposes in her child's apprenticeship for adulthood and that not only is play essential for attaining emotional maturity but, to quote the author, it is the normal means of acquiring many adult skills. It is during later infancy, when the child can crawl or toddle and its range of play is increased, that the greatest demands are made on her understanding and patience.

Then, he says, she will have to reach a compromise between allowing the infant freedom for exploratory and messy play on the one hand, and preventing him from damaging himself (or creating too much household havoc) on the other. This is most likely to be achieved if she realizes clearly that his explorations are an essential part of his development, and that if they are unnecessarily and continuously frustrated, both his initiative and his relations with herself will suffer.

'In a cultural setting in which there is very seldom an older child at liberty to help with supervision of the exploring toddler, the demands made on a conscientious mother are apt to be very heavy, and one sympathizes with the mother who finally climbed into the play-pen herself and allowed the infant the free run of the garden.'

Creative play merges logically into productive work, and herein lies one of the many problems facing parents nowadays. In most unsophisticated cultures, writes Dr. Ellis, the child will have ample opportunity of seeing both the parents at work. The boy will often start by imitating his father's occupation in a play situation, and gradually be drawn into co-operation and apprenticeship. Similarly, the little girl will first imitate and then help her mother in the home or fields. The more sophisticated countries are rapidly making any similar transition impossible. *It is exceptional now, he adds, for boys to see their father at work, and often they have little conception of what he does between leaving home in the morning and returning tired in the evening.* An increasing number of mothers of young children are entering full-time employment, so that the girl also may grow up with little first-hand experience of domesticity, home-making, or care of younger children.

Another problem arises from the limited opportunity for productive work for the child before he reaches the age of 15. What is rightly described by the author as the 'appalling exploitation of child labour' during the nineteenth century was followed by a violent reaction 'which has gone to the opposite extreme'. The child is not only protected by legislation against exploitation in industry, but he is forced to spend a minimum of 10 years within a system of formal education which for many children proves unsatisfying and ill-balanced. And with Dr. Ellis parents might well ask 'whether exclusive concentration on full-time education until middle teenage is not in fact depriving the child of the earliest stages of adult responsibility and status, and so retarding some part of his social development. *The question might be superfluous if there were not a manifest increase in juvenile delinquency and maladjustment, and at the same time plans for extending compulsory schooling for a further year*'.

One further very important factor discussed by Dr. Ellis is the present trend toward earlier sexual development and the consequent shortening of childhood.

'For the girl', he writes, 'it adds to the risks of pregnancy before marriage, and for the boy it lengthens the frustrating period during which he is sexually mature but is not regarded as a adult. The school system which is based primarily on chronological age and intelligence rather than physical maturity is faced with the problem of educating together completely heterogeneous groups of boys aged 14 to 15 years of whom the majority are pubescent, but which contain almost equal minorities of those who are completely immature (non-pubescent) and those who are adolescent. A similar problem arises with girls aged 12 to 13 years. In co-educational schools the two problems are superimposed. Since the child and adolescent require different handling and respond differently to adult authority, it is not surprising that an educational system which virtually ignores physical maturity in its grouping is meeting difficulties which are frequently unsolved and which are passed on to society when the teenager leaves school.'

Health in Childhood, according to the foreword, has been written for the benefit of the 'man in the street' or, one might add, for the parents of the little boy who lives down the lane. It might also come as a timely

reminder of the danger arising from the present unequal utilization of world food resources. Dr. Ellis, who has studied child health in all its aspects at first-hand in West Africa, South-east Asia and elsewhere, says that this inequality applies not only between country and country, but in backward areas where problems of food transport and storage have not been solved, between neighbouring localities, and between 'fat and lean' seasons . . . *The overriding question is now whether food-production can even keep pace with the steadily increasing number of mouths to be fed.*

Early Identification of Emotionally Handicapped Children in School. By ELI M. BOWER. (Pp. xiii + 120. 44s.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

Eli Bower is the Deputy Director of Liaison and Prevention of the California State Department of Mental Hygiene. This high-sounding and somewhat ambiguous title foreshadows the unique quality of this small monograph.

I have rarely found a book on a familiar subject to be so difficult or occasionally so startling to read. It purports to 'present a usable and useful method by which teachers can be helped to be more effective "suspecticians" about the emotional development of children'. It describes the emotionally handicapped child as one 'who is unable or will be unable to take the slings and arrows of life without caving in, becoming immobilized or exploding'. The problem, says the author, in judging the adjustment capacities of a pupil is 'how to synthesize the different kinds of information and put the various perceptual parts, like Humpty Dumpty, back together again'.

In the midst of this can be found a description of a project to define simple tests by which the class-room teacher can identify emotional problems early enough for successful methods of treatment to be undertaken—a most important task.

In 200 classes 5,500 children were subjected to a complex series of tests which according to the author (statistical tables are to be found in another publication) enabled the teachers to spot a large proportion of the disturbed children. The significant pointers were found in three questionnaires:

(*a*) *Teachers' Rating Scale*—ordinary comments on attainments and a five-point behaviour scale.

(*b*) *Self-evaluation.* This consists of two tests.

(1) A booklet called 'Thinking about Yourself' is distributed to each child. In answer to each of 53 statements, he is asked to choose one of eight responses, e.g.

This boy thinks his mother doesn't like him.
Are you like him always, frequently, seldom, never?
or Do you want to be like him, always, etc.?
This boy would rather play with girls than boys.
Are you like him?

(2) Another evaluation is made by a questionnaire called 'A Class Play'. About 15 possible roles are outlined and the child is asked
Which two parts would you like to play best?
Which two would the children in the class choose for you?
Which would the teacher pick for you?
Which would your best friend pick for you?
The parts all carry heavily positive or negative moral qualities, e.g. a true friend, a mean, bossy sister, a person who is very smart and usually knows the answers. (No score for originality if you would rather be a mean cruel boss, or the laziest person in the world.)

(*c*) *Peer perception*, i.e. what children think of each other. For this, the Class Play is also used and each child is invited to choose a complete cast from among his class mates.

An interesting but superficial discussion of the causes for discrepancy in a child's own perceptions of himself and those of the class follows, and also a description of the marking system whereby higher scores are given for negative choices. The children in a class are ranked in order for each of these three tests and those who appear near the top in two out of the three lists are considered to be emotionally disturbed.

To conclude, 'This process of screening may be seen as one way of providing the teacher with consensual valuation à la Sullivan, confirmation or rejection of a hypothesis à la John Dewey or obtaining a clue to the mystery of a child's behaviour à la Holmes (Sherlock, not Chief Justice)'.

Those who find questionnaires useful will probably prefer to use those of D. H. Stott and his team in Bristol. Personally I doubt if any backward and disturbed child in the ordinary English school would ever be able to complete these tests, one of which requires not only the ability to read and retain 15 possibilities, but the ability to make a definite and thoughtful choice. Most neurotic children suffer from the disease which another American book describes as 'abulia', an inability to make decisions.

I do not feel, however, that the readers of this journal need spend any time making a decision about this book. My advice is definite. It is not worth 44s., and I am surprised that Blackwell Scientific Publications think it is.

PRINTED IN GREAT BRITAIN BY HEADLEY BROTHERS LTD 109 KINGSWAY LONDON WC2 AND ASHFORD KENT